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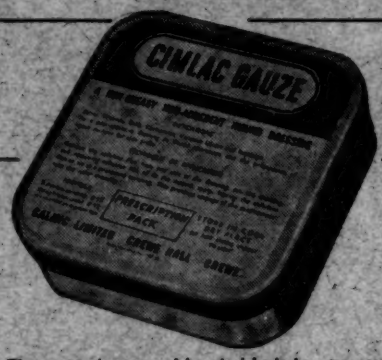

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 19 1950

CLINICAL TRIALS OF ANTIHISTAMINIC DRUGS IN THE PREVENTION AND TREATMENT OF THE COMMON COLD

REPORT BY A SPECIAL COMMITTEE OF THE MEDICAL RESEARCH COUNCIL*

The investigations of Brewster (1947, 1949), Gordon (1948), Murray (1949), Arminio and Sweet (1949), Phillips and Fishbein (1949, 1950), and Tebrock (1950) suggested that antihistaminic drugs had beneficial effects in the prophylaxis and treatment of the common cold. On the other hand, these observations could not be confirmed by Paton, Fulton, and Andrewes (1949), Hoagland, Deitz, Myers, and Cosand (1950), Feller, Badger, Hodges, Jordan, Rammelkamp, and Dingle (1950), and Cowan and Diehl (1950). A critical review by the Council on Pharmacy and Chemistry of the American Medical Association (1950) cast serious doubt on the validity of the conclusions and the interpretation of the results of some of the earlier investigations, referred to above, which had seemingly shown favourable effects.

In view of the great practical importance of the favourable findings, if confirmed, the Medical Research Council undertook, at the request of the Ministry of Health, to investigate in this country the value of the treatment. A special committee was appointed early in 1950, and the results of the tests arranged by the committee are reported here.

The trials have been of two kinds : (1) small-scale tests of two powerful antihistaminic drugs—promethazine hydrochloride ("phenergan," May & Baker, Ltd.) and chlorocyclizine hydrochloride ("histantin," Burroughs Wellcome & Co.)—in the prevention of inoculated colds in volunteers at the Common Cold Research Unit, Harvard Hospital, Salisbury ; and (2) large-scale trials of the much weaker antihistaminic thonzylamine (also known in America as "neohetramine" or "anahist") for the treatment of colds occurring naturally among volunteers drawn from the general adult population—workers in the Civil Service, industrial establishments, universities, and the like (see Appendix).

I. THE PROPHYLACTIC EXPERIMENT AT SALISBURY†

The object of this experiment was to see whether antihistaminics given before, and for a few days after, nasal instillation of common-cold washings to human volunteers would prevent the development of a cold. Histantin and phenergan were selected as the drugs for test, as the antihistaminic activity of both was known to be high. The volunteers were isolated in pairs throughout the trial—in the same way as has previously been described by Andrewes (1949). Half the subjects received the drug under test, the other half received dummies indistinguishable from it and containing ¼ gr. (16 mg.) of phenobarbitone. It was felt that the latter would, in the dosage employed, have a mild sedative effect and so be acceptable as a control medication against which the efficacy of the antihistamine could be measured. Tablets were given at approximately 10 a.m. and 7 p.m., swallowing being supervised by the matron. Two members of a pair were given the same substance. Whether they were to be given the drug or the dummy was decided randomly, and neither the patient nor the clinical observer knew which any particular patient had received.

Trial 1 : Histantin (January 18–28, 1950)

A 50-mg. tablet of histantin (or of the dummy) was given twice daily, beginning 48 hours before the cold inoculation and continuing until 72 hours after it. The virus inoculum was a 1 in 3 dilution of an unfiltered washing from patient G., who had developed a cold after receiving passage material from one of the Common Cold Research Unit's "pedigree" strains, Harrow. The results are shown in Table I. The incidence of colds is seen to be the same in the treated and control groups ; there was no clinical difference from the usual course of experimental colds. One spontaneous cold developed in a subject who had been taking histantin for 24 hours ; a similar case occurred in the control group.

TABLE I.—*Results of Trial 1*

Drug Administered	Cold	No Cold
Histantin	4*	4
Control tablet	4*	4
Total	8	8

* Includes one spontaneous cold developing during quarantine period before inoculation.

Trial 2 : Phenergan (February 1–11, 1950)

A 20-mg. dose of phenergan (or of the dummy) was given twice daily, beginning 60 hours before virus inoculation and continuing for 72 hours after. Two test viruses were used —unfiltered G diluted 1 in 3, as in Trial 1, and a filtrate

*The membership of the committee was as follows: Dr. F. H. K. Green (chairman), Dr. C. H. Andrewes, Professor W. A. Bain, Professor A. Bradford Hill, Dr. W. C. Cockburn, Dr. P. D'Arcy Hart, Dr. J. Faulkner, Dr. N. L. Lloyd, Group Captain T. C. MacDonald, Dr. L. G. Norman, Dr. J. P. Sparkes, Dr. T. Sommerville, and Dr. J. A. Harrington (who was appointed secretary and co-ordinated the trials).

†Members of the staff concerned with this investigation were C. H. Andrewes, T. Sommerville, K. R. Dumbell, and J. S. Porterfield.

Table II.—*Results of Trial 2**

Drug Administered	Cold Washing	Cold	No Cold
Phenergan	G	5	0
	Pool 82	2	2
Control	G	3	4
	Pool 82	1	3

* In the phenergan experiment two volunteers of opposite sex were unpaired; these were treated as singletons, one getting the drug and one not. In addition one volunteer and her partner inoculated with the G virus have been excluded since she developed influenza in the course of the experiment.

of pool 82 (also virus of Harrow passage series). Table II shows the results. As in Trial 1 there is no evidence of prevention with the antihistaminic drug.

Side-effects

Subjects were not warned that some side-effects of the drugs might be apparent, but may well have read of this possibility in the lay press. In the first trial, of the eight persons taking the drug only one complained of "fuzziness in the head" half an hour after her fourth dose of histantin; it lasted ten minutes. In the second trial four patients complained of drowsiness; two were in the phenergan and two in the control group. In assessing the significance of this low incidence of side-effects it must be remembered that the volunteers in this trial were leading a very leisurely existence and were under no kind of strain.

Discussion

Some claims to a beneficial effect of antihistaminics in curing colds have emphasized the need for beginning treatment within a few hours of onset. It is thus particularly noteworthy that the results at Salisbury with experimental colds showed no effect even when the drugs were given for two to three days *before* infection. Clinical observation of the volunteers revealed no difference in the nature and duration of experimental colds in those who received antihistaminic treatment and those who did not. The results with the two antihistaminics tested were clear cut, and there seemed to be no good reason for repeating the experiment with other drugs of a similar kind.

II. LARGE-SCALE THERAPEUTIC FIELD TRIAL

Plan of Investigation

To assess the value of antihistaminic drugs in the treatment of the common cold it was necessary to compare the experience of treated individuals with that of a similar group not treated; for this purpose it was decided to plan the inquiry on similar lines to those adopted by a committee of the Council in investigating the value of patulin for the same purpose during the war (*Lancet*, 1944, 2, 373).

Choice of an Antihistaminic for Test.—The antihistaminic drugs vary considerably in their properties, potency, and toxicity, but it clearly was impracticable to carry out field tests of more than one product if sufficiently large groups for statistical analysis were to be obtained within a reasonable period. The available evidence indicated that thonzylamine would be the most appropriate choice in the first instance, as it was generally accepted as having a low toxicity (Friedlaender and Friedlaender, 1948; Criep and Aaron, 1948; Schwartz, 1949) and had been claimed as very effective against the common cold by Arminio and Sweet (1949) and Tebrock (1950).

Organization of Trials at Individual Centres.—The supervision and conduct of the investigation at the individual centres were carried out by medical officers who had been visited by the secretary of the committee and instructed in the standard procedure proposed; at some centres the conduct of the test was delegated to a trained industrial nurse working under the supervision of a medical officer. The existence of the trial was brought to the notice of potential volunteers by means of posters, notices, etc., the details of publicizing the scheme being left to the medical officer in charge. Volunteers were told of the experimental nature of the inquiry and the desirability of attending for treatment as soon as possible after the onset of symptoms of a cold.

Selection of Cases.—Admission to the trial was limited to volunteers over the age of 15 years in whom there was good evidence of the presence of the common cold. As it was important to obtain uniformity in different areas, the following definition of a common cold was given as a guide to the observers: "A catarrhal inflammation of the upper respiratory passages usually without pyrexia but with a watery or mucous discharge from the nose and associated with sneezing, fullness in the head and nose, and sometimes with cough, headache, sore throat, hoarseness, and running eyes." Reliance was placed mainly on the subjective diagnosis, and cases were accepted on the basis of the patient's description of his symptoms; clinical examination, other than the recording of temperatures, was carried out only to exclude other conditions. All volunteers whose conditions fell into any of the following categories were excluded: chronic catarrh or sinusitis; acute tonsillitis; suspected influenza; any person whose temperature was found to exceed 100° F. (37.8° C.); those who, on inquiry, seemed likely to have taken an antihistaminic drug for any purpose within the previous week; those with a *present attack* of hay-fever or allergic rhinitis. Persons with a *previous history* of allergic states were included, but a note to this effect was made in the appropriate column of the record sheet.

Design of Trial

To ensure that no bias could enter into the assessment of results it was essential that neither the patient nor the investigator should be aware whether antihistaminic tablets or control tablets had been given in a particular case. For this purpose, those who were to be treated and those who were to be "controls" were prearranged in random order by the use of random sampling numbers, with the one restriction that each batch of 50 volunteers should include 25 treated (T) and 25 controls (C) (a restriction not known at the centres).

These lists were numbered consecutively, so that, for example, a series might run as follows: 1T, 2T, 3C, 4T, 5C, 6C, and so on, randomly. Such lists were constructed, in the Council's Statistical Research Unit, for each centre. Record sheets and cartons containing the appropriate tablets were then marked (in the Statistical Research Unit) with the serial number—namely, 1, 2, 3, 4, 5, 6, etc., but with no reference to (T) or (C)—and sent to the local centres; thus at the local centre one carton and one record sheet, *the serial numbers of which corresponded*, were used for each patient. They were used in strict order of serial number; thus if the last patient on one day was recorded on record sheet "15" and received tablets from carton "15," the first patient on the next day was recorded on record sheet "16" and received tablets from carton "16." The key to the identity of the serial numbers was kept centrally and secret until the end of the investigation.

This somewhat novel method was adopted in place of the more usual one of merely labelling one product X and the other Y and giving them in random order, in view of the side-effects to be expected with the antihistaminic drug. If decisive side-effects were observed with even one patient then the nature of X (and Y) would ever after be known (or suspected). With the method chosen the identity of one carton might well be suspected in the patient with

side-effects, but no evidence would thereby be given regarding the treatment of any other patient.

Course of Treatment

At the first attendance the medical officer, having satisfied himself that the patient was suffering from a common cold and was not within one of the excluded categories previously defined, completed Part A of the record sheet (reproduced here) and then proceeded to dispense the tablets.

Each patient, it was laid down, should receive one tablet three times a day for three days—that is, a total of nine tablets. The individual and numbered carton for each patient held three envelopes, each containing three tablets: one envelope was issued each day—that is, on reporting, on the next day, and on the day following that. Antihistaminic tablets contained 50 mg. of thonzylamine; control tablets contained 5 mg. of quinine sulphate in a lactose base. All tablets were sugar-coated, and those which contained the antihistaminic were indistinguishable in appearance from those which did not. Volunteers were told to swallow the tablets whole, to remove the possibility of detection by taste if they were bitten or chewed. Each patient was given an instruction leaflet (explaining the details of the treatment and follow-up) and a note to hand to his family doctor if the latter was consulted during the period of the test.

Follow-up and Assessment of Progress

Patients were instructed to report progress at the end of 24 hours, 48 hours, and after a week. At these attendances the volunteers were requested to state quite frankly whether they thought the treatment given had been effective; assessments of progress were recorded by ringing the words "cured," "improved," "unchanged," "worse," or "recurred" as appropriate. The definitions of these categories had been laid down as follows:

"*Cured.*"—Only those persons who, after questioning, are found to be *completely* free from symptoms and who, on examination, are found to be without objective signs.

"*Improved.*"—Persons who, on questioning and examination, are found to be improved but not cured since the previous examination.

"*Unchanged.*"—Persons in whom, on questioning, the symptoms and signs are found to be unchanged since the previous examination. (*All cases in which there was doubt regarding progress were included in this category.*)

"*Worse.*"—Persons in whom, on questioning and examination, the symptoms and signs are found to have increased since the previous examination.

"*Recurred.*"—Patients, previously classified as "cured," and who report with another cold within 14 days of recovery from the previous one.

Assessment of Side-effects.—Direct questions about side-effects were avoided during treatment lest the investigator

---

Trial Centre

RECORD SHEET

Trials of Antihistaminic Drugs in the Treatment of the Common Cold

(MEDICAL RESEARCH COUNCIL)

Serial Number

Surname (BLOCK CAPS) Initials: | Mr. Mrs. Miss | Age (years) | Clock No. | Department | Occupation

A FIRST EXAMINATION (*To be filled in by a doctor: please put a ring round the appropriate items*)

Has patient been previously treated in these trials? Yes No

Is there any previous history of: Hay-fever Allergic Rhinitis Asthma

Other Allergic Manifestations (*State nature*):

Date of first examination | Time

Duration in days of Head Cold before first examination: ½ 1 1 2 3 4 5 6 7 or more days

Blocked Nose Fullness in Head Sneezing Sore Throat Hoarseness Cough Headache Feeling Ill

Nasal Discharge: Watery Mucoid Purulent Temperature (if taken).....

Are you satisfied that this is a case of Common Cold? Yes No Uncertain

B (Enter progress at 24 hours, 48 hours, and after a week) PROGRESS RECORD (*Please put a ring round appropriate items*)

Date	Time	Number of Tablets Since Previous Recordings	Progress	Temperature (if taken)	Doctor's Comments
			Cured Improved Unchanged Worse		
			Cured Improved Unchanged Worse Recurred		
			Cured Improved Unchanged Worse Recurred		
			Cured Improved Unchanged Worse Recurred		
			Cured Improved Unchanged Worse Recurred		

[SEE OVER

Reverse Side of Record Sheet

SIDE-EFFECTS

(*Please do not ask* DIRECT QUESTIONS *about specific side-effects as this may give misleading results*)

1. Has the treatment agreed with the patient? Yes No
2. If "No," what symptoms does the patient attribute to the tablets? (*State nature and severity as "mild," "moderate," or "severe"; and date of occurrence*)

Off work* from.....to..... Reason:

* (*Delete if not off work during trial*)

ANY FURTHER COMMENTS

might surmise from the answers whether the patients were on the antihistaminic or the control treatment. Where, however, side-effects were spontaneously complained of, details were noted, including the nature, date of onset, and severity. In all cases the patient was asked at his *last* attendance, and after the assessment of progress, whether the tablets had affected him adversely in any way; if the answer was in the affirmative the symptoms attributed by the patient to the tablets were noted.

Results

These therapeutic trials were set up at 19 widely distributed centres with a total population of approximately 58,000. They were carried out in each area between the middle of March and the middle of May, 1950, though not invariably over the whole of that period.

In total, 1,550 volunteers at the various centres were treated in the investigation—775 with the drug and an equal number with the control tablets. However, 394 record sheets had subsequently to be rejected from the analysis for such reasons as failure to complete the treatment or to report progress on the required days. These rejects came about equally from the treated and control groups (196 and 198 respectively), and thus show no differential bias. Deducting the rejects, 1,156 record sheets were available for analysis—579 for patients who received antihistaminic treatment and 577 for patients who had the alternative treatment. Since analysis of the results from each centre revealed no significant difference between them, only the combined results from all centres need be given here. It may also be noted that a special analysis was made according to the number of records that had to be rejected. The centres were grouped in three categories: under 10% of records rejected, 10–19% rejected, 20% or more rejected. No differences in results were revealed, showing again that the lapses did not bias the inquiry.

The comparable nature in regard to initial symptoms of the volunteers who received antihistaminic treatment and those who did not is shown in Tables III and IV. It will be seen that the method of random allocation used resulted in two groups which were closely alike in relevant respects.

The results at the end of the first day, second day, and one week for different durations of colds before treatment are given in Table V. None of the differences is individually statistically significant for each duration of cold before treatment, and indeed the similarity in response of the two groups seems more remarkable than any dissimilarity. For instance, of those who came for treatment within the first day of their onset of symptoms, 13.4 and 13.9% of the treated and controls, respectively, reported a cure on the second day; 48.8 and 46.8% were cured at the end of the week. It may, however, be noted that the treated group had consistently a slightly higher proportion of cured and improved on the first day of treatment than had the controls.

By combining all results, irrespective of duration of cold before treatment, 48.0% of the treated and 42.1% of the control group were found to be improved (including nine treated and five control cases who were cured) at the end of the first day's treatment. The difference, 5.9±2.9, is just significant in a technical sense, but even if it be real it is so small that it clearly has no practical importance. Also, this small difference, it will be seen, vanished on the second day, when, taking all the group together, the proportions of cured and improved were respectively 8.8% and 53.0% in the treated and 8.5% and 51.3% in the control group. Possibly the apparent small difference at the end of the first day's treatment can be accounted for by a slight sedative effect in some few subjects who received thonzylamine or by the unwitting inclusion of some individuals who were suffering from hay-fever or an allergic rhinitis and not from the common cold.

It has been mentioned that volunteers with a present attack of hay-fever or allergic rhinitis were, so far as possible, excluded, but persons with a previous history of allergic conditions were included provided they were believed to be suffering from a cold. From Table VI it will be seen that a previous history of hay-fever, allergic

TABLE III.—*Duration of Cold Before Treatment was Begun*

Duration of Symptoms Before Treatment (in Days)	Persons Given Antihistaminic Treatment		Persons Given Alternative Treatment	
	No.	%	No.	%
½	64	11·1	60	10·4
½	137	23·7	113	19·6
1	180	31·1	213	36·9
2	96	16·6	84	14·6
3	49	8·5	42	7·3
4	22	3·8	25	4·3
5	7	1·2	10	1·7
6	8	1·4	1	0·2
7+	16	2·8	29	5·0
Total	579	100·2	577	100·0

TABLE IV.—*Frequency of Presenting Symptoms at First Visit*

Symptoms	Persons Given Antihistaminic Treatment		Persons Given Alternative Treatment	
	No.	%	No.	%
Watery nasal discharge ..	359	62·0	337	58·4
Mucoid nasal discharge ..	114	19·7	118	20·5
Purulent nasal discharge ..	49	8·5	42	7·3
Blocked nose	321	55·4	307	53·2
Fullness in the head ..	385	66·5	390	67·6
Sneezing	413	71·3	408	70·7
Sore throat	217	37·5	231	40·0
Hoarseness	183	31·6	177	30·7
Cough	242	41·8	226	39·2
Headache	196	33·9	207	35·9
Feeling ill	44	7·6	46	8·0

TABLE V.—*Percentage Cured or Improved at the End of the First Day, Second Day, and One Week for Different Durations of Cold Before Treatment*

Day of Observation		Duration of Cold Before Treatment											
		Under 1 Day			1 Day			2 Days			3 Days or More		
		T (201 Obs.)	C (173 Obs.)	Difference	T (180 Obs.)	C (213 Obs.)	Difference	T (96 Obs.)	C (84 Obs.)	Difference	T (102 Obs.)	C (107 Obs.)	Difference
First day—improved*		47·8	45·1	2·7±5·2	47·2	38·5	8·7±5·0	50·0	40·5	9·5±7·4	48·0	45·8	2·2±6·9
Second day	Cured ..	13·4	13·9	−0·5±3·6	7·8	6·6	1·2±2·6	3·1	4·8	−1·7±2·9	6·9	6·5	+0·4±3·5
	Cured or improved	68·2	64·7	3·5±4·9	58·3	55·4	2·9±5·0	59·4	57·1	2·3±7·4	57·8	62·6	−4·8±6·8
One week	Cured ..	48·8	46·8	2·0±5·2	42·2	37·1	5·1±5·0	31·3	33·3	−2·0±7·0	29·4	36·4	−7·0±6·5
	Cured or improved	80·6	74·6	6·0±4·3	77·8	77·5	0·3±4·5	70·8	79·8	−9·0±6·5	70·6	78·5	−7·9±6·0

T = Antihistaminic treatment. C = Alternative treatment. Obs. = Number of patients observed.
* Including the few patients (9 T and 5 C) who said they were cured on the first day.

TABLE VI.—*Distribution of Results at the End of the First Day, Second Day, and One Week for Persons with a Previous History of Allergic Conditions*

	1st Day		2nd Day		Week	
	T	C	T	C	T	C
Previous history of hay-fever						
Cured	2	—	4	3	6	13
Improved	13	13	13	14	12	12
Unchanged	10	16	8	14	8	6
Worse	3	5	3	3	1	1
Recurred	—	—	—	—	1	2
	28	34	28	34	28	34
Previous history of allergic rhinitis						
Cured	1	—	3	3	3	7
Improved	12	7	10	12	12	8
Unchanged	9	10	10	6	7	4
Worse	3	6	2	2	2	1
Recurred	—	—	—	—	1	3
	25	23	25	23	25	23
*Previous history of other allergic manifestations**						
Cured	—	—	4	5	15	13
Improved	25	17	22	17	20	12
Unchanged	17	10	12	9	8	5
Worse	2	7	6	3	1	3
Recurred	—	—	—	—	—	1
	44	34	44	34	44	34

T = Antihistaminic treatment. C = Alternative treatment.
* Including asthma, urticaria, and other conditions believed to have an allergic basis.

rhinitis, and other allergic manifestations had no striking influence on the results obtained with the treatment, but the numbers in each of the treated and control groups are small. By combining all these allergic manifestations the figures shown in Table VII are obtained.

TABLE VII.—*Percentages Cured or Improved*

	1st Day	2nd Day	One Week
Treated	54·6	57·7	70·1
Controls	40·7	59·3	71·4
Difference	13·9±7·3	−1·6±7·2	−1·3±6·6

There is a suggestion that the antihistaminic drug gave some relief to these subjects during the first day of treatment, but later results do not differ at all.

Side-effects.—Side-effects attributed to the treatment were reported by 121 (20.9%) subjects receiving the test drug, while the comparable figure for those receiving the alternative treatment was 111 (19.2%); details are given in Table VIII. It is most unlikely that the large number

TABLE VIII.—*Side-effects Attributed to Treatment*

Main Symptoms	Persons Given Antihistaminic Treatment	Persons Given Alternative Treatment
Drowsiness, lassitude, listlessness	26	35
Dizziness, giddiness, vertigo	21	13
Headache	21	16
Headache and other nervous symptoms	11	6
Depression with or without other nervous symptoms	2	5
Insomnia	3	1
Gastro-intestinal	13	12
Combined gastro-intestinal and nervous symptoms	8	7
Miscellaneous	16	16
Total	121	111

of side-effects attributed to the alternative treatment can have been due to the small doses of quinine given in the control tablets. It seems much more probable that many of the symptoms described as side-effects were, in fact, symptoms of the cold itself. On the other hand, when, as here, efforts were made to avoid direct questions about specific side-effects, prior knowledge of the possibility of reactions may have led to a spurious increase in their incidence through psychogenic factors.

CONCLUSIONS

In a small but carefully controlled experiment two antihistaminic drugs—promethazine hydrochloride and chlorocyclizine hydrochloride—showed no evidence of having any value in the prevention of experimentally induced colds.

A large-scale clinical trial of thonzylamine in widely separated areas in Great Britain and Northern Ireland, carried out between the middle of March and the middle of May, 1950, showed that, in the dosage employed, this antihistaminic drug had little if any value in the treatment of the common cold.

The committee is greatly indebted to Dr. W. J. Martin, of the Medical Research Council's Statistical Research Unit, for carrying out the statistical analysis of the results, and to the managements, medical staffs, and volunteers in the industrial and Civil Service establishments, universities, and elsewhere for their co-operation and assistance in carrying out the trials. Thanks are also due to Dr. W. E. Chiesman, Treasury Medical Adviser, for much help, and to the Director-General of Medical Services, Royal Air Force, for permitting the inclusion of R.A.F. personnel in the trial. The antihistaminic drugs and control tablets for the experiment at Salisbury were kindly supplied by May & Baker Ltd., and Burroughs Wellcome & Co., and the supplies of thonzylamine used in the therapeutic field trials were specially made for the purpose by May & Baker Ltd., who also kindly provided the control tablets.

APPENDIX

Trials were carried out at the following establishments:

Trial Centres	Medical Officer in charge
Treasury, London	Dr. V. C. Medvei
G.P.O., London	Dr. E. M. Anderson; Dr. O. May
Ministry of National Insurance, Newcastle-upon-Tyne	Dr. S. E. McConnell
University of Leeds, School of Medicine	Dr. J. L. Broadbent
London School of Hygiene and Tropical Medicine	Dr. J. P. W. Hughes
Belfast Corporation	Dr. J. C. Stutt
Lever Brothers and Unilever Limited	Dr. D. S. F. Robertson
Anglo-American Oil Company Limited	Dr. G. J. Murray.
Richard Hodgson and Sons Limited	Dr. E. H. Thierry
Monsanto Chemicals Limited	Dr. H. R. Newman
Marks and Spencer Limited	Dr. Marjory Oldershaw
Harrods Limited	Dr. Margaret Dobbie-Bateman
Stanton Ironworks Company Limited	Dr. D. K. Cowan
I.C.I. Ltd. Metals Division, Birmingham	Dr. N. G. Marr
London Transport Executive	Dr. L. G. Norman
R.A.F. Centres (3)	Group Captain T. C. MacDonald
Central Public Health Laboratory	Dr. J. A. Harrington

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TRIAL OF ANTISTIN IN THE COMMON COLD

BY

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Following American reports of the suppression of symptoms of the common cold by the prompt administration of antihistaminics, it was felt necessary to make a large-scale trial in the United Kingdom, adopting such controls as were practicable, in an endeavour to remove doubt concerning the efficacy or otherwise of the suggested treatment. "Antistin" (2-phenyl-benzyl-aminomethyl-imidazoline hydrochloride), synthesized by Miescher, Urech, and Klaren, of Ciba, was selected as suitable for such a trial because it is an antihistaminic of which favourable reports have been published in the treatment of allergic conditions such as urticaria, angioneurotic oedema, and hay-fever, and it has a comparatively low incidence of side-effects (Meier and Bucher, 1946; Britton, 1947; Overton, 1948).

The plan of the trial was based on that of the Medical Research Council's trial of patulin in the treatment of the common cold. Their report (1944) emphasized the following points in connexion with such a trial :

1. Since there is no reason to believe that the common cold is always or even usually due to the same agent either in sporadic cases or in different epidemics, it is necessary to include a large number of patients at several widely separated places, over a period long enough to exclude the possibility that a single prevalent epidemic is being studied.

2. Since the duration of colds is not constant but varies not only between different epidemics but also between different patients in the same epidemic, there must be a satisfactory series of control cases. This can be done only by ensuring that alternate cases at each centre receive a spurious treatment which to the recipient is indistinguishable from the genuine treatment.

3. The objective signs associated with the common cold are too variable to suffice as criteria of its presence or progress. A cold manifests itself mainly by subjective symptoms, and consequently diagnosis rests mainly upon the statements of the untrained patient.

Method

The trial was carried out in eight factories and one public school. These centres, comprising a total population of over 50,000, were widely scattered throughout the country. Antistin tablets (0.1 g.) and dummy tablets of identical appearance and practically identical taste were used, the latter having the following composition : lactose, 0.085 g.; quinine sulphate, 0.005 g.; starch, 0.031 g.; talc, 0.015 g.; and gelatin, 0.004 g. (The *British Pharmacopoeia* gives the effective dose of quinine sulphate as 0.3 to 0.6 g.)

It was arranged that none of the medical staff at any of the trial centres should be informed which tablets were active and which dummy. In order further to reduce the likelihood of identification, four letters were used instead of two (Q and S being dummy, and R and T antistin). The tablets were packed in cellophane containers, each container of nine tablets bearing one of the above four letters and instructions for taking the tablets.

It was originally intended that each patient should be seen by a doctor, but in three of the smaller trial centres there was none, and in some of the remainder it was impossible for the doctor to see all patients himself. Therefore many of the case record cards were completed by nurses or medical orderlies. Since the record was in the main simply the patient's own account of his symptoms there seemed to be no serious objection to this procedure.

So far as possible the investigation was confined to patients reporting within 24 hours of the onset of a cold. At the first examination, after recording the patient's name, occupation, etc., on a case record card, the relevant items among the following were ringed :

Duration of cold before first examination: 6, 12, 24 hours.
Nasal: Sneezing Discharge (clear, purulent) Obstruction.
Throat: Soreness Irritation Hoarseness Cough.
Head: Fullness Stuffiness Headache Lacrimation.
General: Malaise Pains Feverish.

At one centre, where all cases were seen by the doctor, the presence or absence of the following physical signs was regularly recorded : pharyngitis, laryngitis, tonsillitis, and sinusitis. The above scheme is by no means free from criticism, but it appeared to serve its purpose.

Successive patients received containers of tablets marked Q, R, S, and T, and the appropriate letter was noted on the case record card. Instructions were given to take two tablets at once, and thereafter one tablet every four hours except during the night. The patient was asked to report again after 24 hours, 48 hours, and one week, and at each interview the patient's own opinion whether the cold was cured, improved, or unaffected was recorded. The number of tablets taken was also noted. Not altogether surprisingly, the request to report three times during treatment met with only very partial success. The trial ran from November, 1949, until April, 1950.

Results

Therapeutic trials were carried out in nine centres, and the records of 1,744 patients were received from these centres. The numbers were 866 in the treated group and 877 in the control group, while for one person the group was not recorded. Of the treated group 379 and of the control group 366 reported after 24 hours, 48 hours, and seven days. Records for the remaining patients who reported once or more were completed for the first day after treatment for 318 in the treated group and 344 in the control group, for the second day after treatment for 245 treated and 249 controls, but only 23 treated and 21 controls reported on the seventh day.

The method of alternative allocation to the treated and control groups gave two groups which were comparable with regard to initial symptoms. Table I shows that the

TABLE I.—*Symptoms at First Examination*

	Treated		Controls	
	No.	%	No.	%
Nasal:				
Sneezing	528	61·0	553	63·1
Clear discharge	478	55·2	469	53·5
Purulent discharge	83	9·6	87	9·9
Obstruction	184	21·2	201	22·9
Throat:				
Soreness	283	32·7	233	26·6
Irritation	198	22·9	198	22·6
Hoarseness	155	17·9	139	15·8
Cough	329	38·0	293	33·4
Head:				
Fullness	152	17·6	158	18·0
Stuffiness	358	41·3	370	42·2
Headache	299	34·5	287	32·7
Lacrimation	98	11·3	104	11·9
General:				
Malaise	146	16·9	105	12·0
Pains	79	9·1	91	10·4
Feverish	85	9·8	87	9·9
Physical signs*:				
Pharyngitis	106	12·2	119	13·6
Laryngitis	13	1·5	9	1·0
Tonsillitis	19	2·2	15	1·7
Sinusitis	38	4·4	30	3·4

* Recorded in one factory only.

distributions of symptoms at the first examination were very similar for the two groups.

The results for the patients who reported on each of the three days are shown in Table II. On each day the proportion recovering was slightly smaller in the treated than in the control series, but none of the differences is statistically significant.

TABLE II.—*Results for Patients who Reported on Each of Days 1, 2, and 7*

	Day 1		Day 2		Day 7	
	Treated	Controls	Treated	Controls	Treated	Controls
Cured ..	6	9	56	68	168	163
Improved ..	208	215	213	203	121	120
No effect ..	165	142	110	95	90	83
Total ..	379	366	379	366	379	366
% cured:						
Treated ..	1·6		14·8		44·3	
Controls ..	2·5		18·6		44·5	
Difference ..	−0·9		−3·8±2·7		−0·2±3·6	
% cured and improved:						
Treated ..	56·5		71·0		76·3	
Controls ..	61·2		74·0		77·3	
Difference ..	−4·7±3·6		−3·0±3·3		−1·0±3·1	

The experience of the patients with incomplete records is shown in Table III. In this group the controls also showed a statistically insignificant advantage over the treated.

TABLE III.—*Results for Patients with Incomplete Records*

	Day 1		Day 2	
	Treated	Controls	Treated	Controls
Cured	8	9	31	39
Improved	169	191	127	142
No effect	141	144	87	68
Total ..	318	344	245	249
% cured:				
Treated	2·5		12·7	
Controls	2·6		15·7	
Difference	−0·1		−3·0±3·1	
% cured and improved:				
Treated	55·7		64·5	
Controls	58·1		72·7	
Difference	−2·4±3·9		−8·2±4·2	

No direct or indirect questions were asked concerning possible side-effects. The number of patients who had conditions which they attributed to the treatment was too small for detailed analysis, for only 14 in the treated group and 13 in the control group complained that the tablets had any adverse effects. Most of the symptoms described could in fact have been symptoms of the cold.

Conclusion

A large-scale trial of antistin failed to show that this drug had any effect on the course of the common cold.

We are greatly indebted to the managements and medical staffs of the centres where the trials were carried out, and we should like to thank the following people in particular for their co-operation and assistance: Dr. G. G. Crisp; Mr. L. Ellis, of Messrs. James Townsend and Son, Ltd., Exeter; Dr. T. England, of Messrs. Currans, Ltd., Cardiff; Dr. J. V. Manning, of Messrs. Pilkington Brothers, Ltd., St. Helens; Mr. J. E. Olsen, of the Ministry of Supply, Military Engineering Experimental Establishment, Christchurch; Dr. M. W. Robinson, of Metropolitan Vickers Electrical Co., Ltd., Manchester; Dr. Philip Ross, of the Morgan Crucible Co., Ltd., London, S.W.11; Miss Kathleen Stott, of Messrs. Beatson, Clark and Co., Ltd., Rotherham; and Dr. J. Magill Young, of the Brush Electrical Co., Ltd., Loughborough.

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EARLY CLINICAL MANIFESTATIONS OF DISSEMINATED SCLEROSIS

BY

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The object of this investigation was to determine which clinical features of disseminated sclerosis are of most diagnostic value, with special reference to the paramount importance of early recognition. The report is based on an analysis of 389 cases of disseminated sclerosis, 79 of which were investigated in a medical ward in the Western Infirmary, Glasgow.

Although not directly concerned in this report with the aetiology of disseminated sclerosis, we would suggest, as does McAlpine (1946), that the evidence in favour of the infective nature of the disease is increasing. Such a contention is strengthened by the recent work of Steiner (1941) and of Margulis and his associates (1946). Campbell and his colleagues (1947) and Campbell (1947) re-emphasize the possible relationship between disseminated sclerosis and agricultural exposure, previously referred to by Morawitz (1904), Steiner (1918), Dreyfus (1921), Adams (1923, 1927), and Wilson (1927).

The diagnosis of disseminated sclerosis at an early stage is important from the point of view of treatment. If therapeutic measures are to be of benefit they must be employed before irreparable damage has been inflicted on the central nervous system. This will be equally true if and when the causal agent is known and specific treatment is available for its eradication. As stressed by one of us in 1923, the ideal hope for the future lies in prevention of infection of the individual by detecting the mode of transmission. Ferraro (1944) has suggested that, once the initial aetiological basis is established, additional factors, such as the development of antigens from the white or grey matter, may play a part in the progress of the disease or in its exacerbations. Bailey and Gardner (1940) have shown that antigenic substances can be derived from myelin sheaths. If such an allergic reaction should indeed occur the importance of early diagnosis and treatment is obvious. The most satisfactory standard of diagnosis will entail recognition of the disease at a monosymptomatic stage.

This standard cannot be achieved, however, until disseminated sclerosis is made known to the general public. It is surprising how infrequently the patient communicates the first symptom to a doctor. Unless the lay public are taught to appreciate the potential significance of such symptoms as temporary weakness in a limb, transient dimness of vision, and diplopia the latter part of Buzzard's (1897) criticism, "the full-grown disease is frequently not recognized, the infant disease practically never," must remain justified.

Early diagnosis depends on proper appreciation of the disease process. We would like to stress the concept that in its early stages disseminated sclerosis is a functional nervous disorder. It was emphasized by Head (1920) that "all disease of the nervous system manifests itself

in loss of function." "Functional" is not the antithesis of "organic," and is not a euphemism for "hysterical." Experience has shown that certain signs depend, commonly, on the destruction of particular parts of the nervous system. It must be appreciated, however, that these are, *per se*, signs of deranged function. In the early stages of disseminated sclerosis they may not be proof of irreversible changes in the central nervous system. Since it is perhaps only at this stage that complete cure can be hoped for, the disastrous policy of waiting for multiple signs and symptoms to become apparent is at once obvious. This paper is mainly concerned with emphasizing those symptoms and signs which appeared first in our series, with a view to the earliest possible recognition of the disease.

Diathesis of the Patient

An important aspect of the clinical recognition of disseminated sclerosis is an appreciation of the type of individual most often attacked by the disease. In the past there has been a tendency to study disseminated sclerosis from the point of view of the "seed" to the exclusion of the "soil." The causal agent of what is almost certainly an infective process may be extensively distributed in nature. The occurrence of the disease in a clinically recognizable form would then be conditioned by personal susceptibility, predisposing factors, or exposure to an overwhelming infection. Such a hypothesis presupposes the existence of subclinical forms of disseminated sclerosis. This possibility has been referred to by Schaltenbrand, and quoted by McAlpine (1946). As in neurosyphilis, there can be little doubt that disseminated sclerosis may exist in an asymptomatic form.

In one case in our experience a paretic curve to colloidal gold was noted in a pensioner suffering from hysteria and showing no clinical evidence suggestive of an organic basis. Four years later loss of the abdominal reflexes was noted. Six years after the colloidal-gold observation had been recorded the patient was admitted to hospital suffering from unmistakable disseminated sclerosis.

With regard to personal susceptibility, disseminated sclerosis occurs most commonly in the sympatheticotonic type of individual. This view has been expressed by Adams, Blacklock, Dunlop, and Scott (1924) and by Adams and Sutherland (1948). As pointed out by Purves-Stewart (1945) in another connexion, sympatheticotonia may be localized. McAlpine (1946) suggests that sympathetic stimulation, by causing a vascular disturbance in the central nervous system, may in some instances be responsible for the appearance of clinical signs. It is not unreasonable to suppose that the effects of such stimulation will be most marked in sympatheticotonic individuals. The occurrence of the disease in patients with a frankly vagotonic diathesis is rare in our experience.

In this series the occurrence of the disease in more than one member of a family has been exceptional. This was also the experience of Risien Russell (1910), Bramwell (1917), Adams (1923), and Wilson (1940). On the other hand, Curtius (1933) found more than one case of disseminated sclerosis in 6 out of 56 families investigated. McAlpine (1946) found a familial incidence in 5% of 143 cases, and Brain (1947) considers that some 5–10% of cases of disseminated sclerosis have a near relative similarly affected. In one case in our series, from a mixed farm in Ayrshire, the patient's father and uncle had died from disseminated sclerosis, whilst his cousin living on an adjacent farm was probably similarly affected. This series of four cases shows common familial and occupational factors.

Predisposing Factors

In 127 cases (32.6%) one or other of four factors preceded the first symptoms of disseminated sclerosis by a short period of time. In no instance did this exceed six months. By so doing, they might reasonably be regarded as predisposing to the illness. These factors were febrile illness (14.4%), trauma (10.5%), pregnancy (4.5%), and emotional upset (2.8%). The association of one of them together with a symptom such as weakness in a limb or diplopia should suggest the possibility of disseminated sclerosis.

Infection

A relationship between disseminated sclerosis and infection has been noted by many workers. Head (1920) observed that disseminated sclerosis not unusually begins with short attacks of what is called "influenza." Bramwell (1917) found this relationship in 28 of his 200 cases (14%). Wilson (1940) and McAlpine (1946) suggest 5% as the possible figure. As a transitory febrile illness may be readily forgotten by the patient, the value of statistical evidence on this point is difficult to assess. Brain (1947) grants that such an illness may be reasonably regarded as a predisposing factor, but considers the cause of the pyrexial reaction to be unknown. Collier and Adie (1933) emphasized the possibility that in some cases this reaction may be a febrile phase of disseminated sclerosis itself.

By analogy with syphilis it was thought that a febrile onset might be associated with a long latency of infection subsequent to the initial manifestation. Thus, Mattauschek and Pilcz (1913) and Browning and Mackenzie (1924) have observed that the course of syphilitic infection may be modified by an intercurrent infection. This possibility was investigated by relating the mode of onset to the duration of the period before the patient presented for treatment. The results obtained suggest that a febrile onset does not materially influence the subsequent course of the disease with regard to latency of infection or progression of the disease process. Of the 56 cases which gave a history of febrile onset, 13 (23.2%) presented for treatment within one year of the first recognizable manifestation of the disease, and 35 (62.5%) within five years. In the 293 cases in which no history of febrile illness was obtained the corresponding figures were 56 (19.1%) and 173 (59%).

Trauma

In 41 (10.5%) of the 389 cases there was a history of either accidental or surgical trauma occurring shortly before the first manifestation of disseminated sclerosis. In a further considerable number of cases a history of trauma preceding an exacerbation was obtained.

This relationship is noted, amongst others, by Marie (1895) and by Adams, Blacklock, Dunlop, and Scott (1924). It appears to exist in 5–10% of cases of disseminated sclerosis (Brain, 1930, 1947). Thus Bramwell (1917) noted the influence of trauma in 17 (8.5%) of 200 cases, von Hoesslin (1934) in 59 (11.4%) of 516 cases, and McAlpine (1946) in 8 (5.6%) of 142 cases.

The mode of action of peripheral trauma as a predisposing factor is not known and the various theories will not be discussed. It is worthy of mention, however, that Browning and Mackenzie (1924), observing that the existence of latent periods in disease is not peculiar to syphilis, consider that trauma may give rise to disturbed relations between the patient and organisms which have already been present for some time without causing an active lesion. In disseminated sclerosis it is possible that trauma may act by adversely influencing the antigen–antibody balance

mechanism in the central nervous system. Klauder (1947), investigating the relationship of trauma and herpes zoster, has afforded some evidence that trauma may light up a latent virus infection.

Pregnancy

The first symptoms of disseminated sclerosis occurred after childbirth in 19 (8.8%) of the 216 female cases. Many authors have referred to the deleterious effect pregnancy and parturition have on this illness. Mention of this is made by Gowers (1893). Risien Russell (1910) observed that pregnancy or parturition may be responsible for relapses or more rapid progress of the disease, and stated that the first symptoms of the malady are not infrequently observed in these instances.

The National Multiple Sclerosis Society (1947) considers that the onset of the disease or a relapse is precipitated in about 40% of female patients who become pregnant. Walshe (1947) refers to the possible ill effects of pregnancy on disseminated sclerosis, but considers that it is not uniformly deleterious, while Wilson (1940) emphasizes the difficulty of establishing a causal nexus between the two. We would suggest that pregnancy in disseminated sclerosis should be regarded as avoidable trauma, and that the occurrence after parturition of a symptom referable to dysfunction of the central nervous system calls for the closest clinical examination.

Emotional Upset

An emotional upset such as grief, worry, or fright preceded the onset of disseminated sclerosis by a short period in 11 cases (2.8%). This relationship has been referred to by Risien Russell (1911), Bramwell (1917), McAlpine (1946), the National Multiple Sclerosis Society (1947), and Adams and Sutherland (1948). Emotional upset may act by "accentuating or evoking phenomena previously existing" (Risien Russell, 1910) or by "reducing resistance" (Wilson, 1940). Emotional reaction may produce stimulation of the sympathetic nervous system, resulting in localized vascular phenomena. It is important to note that in this series patients were not questioned specifically about the occurrence of an emotional upset. The 11 cases concerned volunteered the information, and a note to this effect was made in the case record.

Age and Sex Incidence

Only the age incidence can be regarded as being of diagnostic significance. As will be seen from Table I, 271 (69.7%) cases were in the third and fourth decades of life. It is relatively infrequent for the first symptom of disseminated sclerosis to occur in a patient under 20 or over 45 years of age.

TABLE I.—*Age Incidence at Onset of Disease in 389 Cases of Disseminated Sclerosis*

Age at Onset in Years	Private Series		Hospital Series		All Cases	
	No.	%	No.	%	No.	%
Under 20 ..	22	7·1	5	6·3	27	6·9
20–24	48	15·5	10	12·6	58	14·9
25–29	56	18·0	19	24·1	75	19·3
30–34	61	19·7	19	24·1	80	20·6
35–39	46	14·8	12	15·2	58	14·9
40–44	33	10·7	11	13·9	44	11·3
45–49	14	4·6	1	1·3	15	3·9
50	11	3·5	2	2·5	13	3·3
Not stated ..	19	6·1	—	—	19	4·9
Total ..	310	100	79	100	389	100

In this country female cases slightly predominate. Our figures of 216 (55.5%) female cases and 173 (44.5%) male cases are in accordance with results previously reported by Bramwell (1917), Adie (1937), Wilson (1940), and Brain (1947). Neither the age nor the sex of the patient was found to influence materially the initial symptomatology, with the exception that retrobulbar neuritis predominated in the younger age groups and motor weakness in the older. Thus in the 20–29 years age group of 133 patients, 28 (21%) suffered from transient loss or dimness of vision as a first symptom. In comparison, the 40–49 age group of 59 cases had four cases (6.8%) so affected. Similarly, paresis of one or more limbs was the initial manifestation of the disease in 61 (45.9%) cases in the 20–29 years age group, and in 37 cases (62.7%) of the 40–49 years age group.

Symptomatology

As emphasized by Adie (1932), the onset of disseminated sclerosis is sudden, if by "onset" the appearance of the earliest symptom is referred to. The first symptom is generally attributable to a single lesion in the white matter of the central nervous system. In most cases the initial symptom, after persisting for a variable time, disappears. This is followed by a more or less complete remission, during which time the patient feels in normal health.

An appreciation of those symptoms which suggest the onset of disseminated sclerosis is of fundamental importance. The earliest manifestations in 389 cases are recorded in Table II. It is apparent that the common early symptoms are weakness in one or more limbs (51.4%), visual upset (26.8%), paraesthesiae (8.7%), vertigo (3.8%), and upset of micturition (2.8%). One or other of these symptoms was the earliest manifestation of disseminated sclerosis in 93.5% of cases. The figures obtained differ in no significant manner from those previously recorded by Wilson (1940), who reviewed the initial symptomatology in 539 cases from four series.

TABLE II.—*Initial Symptoms in 389 Cases of Disseminated Sclerosis*

Symptoms	No.	%
Weakness in one lower limb	90	23·1
Weakness in both lower limbs	73	18·8
Temporary dimness or loss of vision in one eye	54	13·9
Diplopia	50	12·9
Paraesthesiae	34	8·7
Weakness in one upper limb	19	4·9
Weakness in one lower and one upper limb	16	4·1
Vertigo	15	3·8
Upset of micturition	11	2·8
General debility; exhaustion; weakness	4	1·0
Mental confusion; inability to concentrate	3	0·8
Pain in leg(s)	3	0·8
Pain in back	3	0·8
Weakness in all four limbs	2	0·5
Epileptiform attacks	2	0·5
Dysarthria	2	0·5
Unilateral facial paralysis	2	0·5
Loss of sensation over side of face; weakness of mastication	2	0·5
Staggering gait	2	0·5
Vomiting	1	0·3
Nervousness	1	0·3

We should like to make further reference to the occurrence of acute retrobulbar neuritis in disseminated sclerosis. Owing to the long remission which may follow transient dimness or loss of vision in one eye, the accuracy of statistical evidence on the subsequent development of disseminated sclerosis after retrobulbar neuritis is difficult to assess. Gunn (1904) found that of 233 cases of primary retrobulbar neuritis 51 (21.9%) were due to disseminated sclerosis. Marburg (1920) reported that 14 (58.3%) out of 24 cases of retrobulbar neuritis subsequently developed disseminated sclerosis. Weill (1923) investigated 22 cases of retrobulbar neuritis; 12 were found to be suffering from disseminated sclerosis, and a further five subsequently developed the disease.

Adie (1932) examined 70 cases of retrobulbar neuritis within one or two weeks of onset. He found 31.3% of

these cases to be suffering from disseminated sclerosis, and in a further 41.8% the diagnosis was probably disseminated sclerosis. Thus in only some 26.8% was there no other suspicious symptom and no definite sign of organic nervous disease. Adie (1929) emphasized that "there is only one known, proved, common cause of this condition, and that is disseminated sclerosis." This fact was previously stressed by Adams (1927). We would suggest that as the primary chancre or secondary rash of syphilis need not portend neurosyphilis, so retrobulbar neuritis need not progress to widespread involvement of the central nervous system. It is nevertheless probable that almost every case of otherwise idiopathic retrobulbar neuritis is due to the causal agent of disseminated sclerosis.

Emphasis has rightly been placed on those initial symptoms which occur most commonly, and, by so doing, to some extent suggest the diagnosis. We would stress, however, that in some 5% of cases the first symptom may not in itself be suggestive of the onset of disseminated sclerosis. Thus we have encountered, as the first manifestation of the disease, mental confusion, pain in the back, pain in legs (each three cases, 0.8%), epileptiform attacks, facial paralysis, loss of sensation over side of face, dysarthria, and staggering gait (each two cases, 0.5%).

Potential Relationship Between Occupation and Initial Symptoms.—This aspect was investigated, but with the exception of brain workers difficulty was experienced in classifying the occupation of the 389 patients into clear-cut divisions. It is interesting, however, that the clearly defined group of brain workers showed the highest incidence of retrobulbar neuritis. It is known that in tabes dorsalis occupational overstrain of the eyes predisposes to optic atrophy.

Potential Relationship Between Initial Symptoms and Latency of the Disease.—Adie (1932) observed that very long remissions "up to 20 years or more" are not uncommon where retrobulbar neuritis is the first symptom. He considers, however, that similar remissions are not common after other modes of onset. This question was investigated by relating initial manifestations to the duration of the period before the patient reported for treatment. In some instances this period will refer to the rate of progress of the disease rather than to absolute latency of infection. Despite this, it seemed to constitute a reasonable basis for investigation.

A latent period of 15 years or more followed the initial symptoms in 31 cases (7.9%). The only initial symptoms to be followed by a latent period of such duration were dimness or loss of vision in one eye in 8 cases (14.8%), paresis in 19 (9.5%), and diplopia in 1 (2%). It would therefore be reasonable to suppose that, since these symptoms may be followed by such a long latent period in some instances, they may be the sole manifestation of disseminated sclerosis in a lifetime. As Adie (1929) suggested in connexion with retrobulbar neuritis, "If a remission should last for 24 years, why not 54?" It should therefore be stressed that a prolonged remission following the initial symptom does not in any way invalidate the diagnosis of disseminated sclerosis. A further manifestation may occur at any time, or the remission may last for a lifetime.

Later Symptomatology.—Table III lists the main symptoms in 389 cases on presenting for treatment. Most of these patients were suffering from multiple symptoms; in a few instances the disease was fully established. A noticeable feature is the frequency with which upset of micturition occurs in the later stages of the disease. As an initial symptom bladder control was defective in only 11 cases (2.8%). In comparison, on presenting for treatment 173 patients (44.5%) complained of some defect of micturition. In view of the nature of this paper further discussion on late symptomatology is unnecessary.

TABLE III.—*Main Symptoms in 389 Cases of Disseminated Sclerosis on Presenting for Treatment*

Symptoms	Patients Affected No.	%
Paresis of limb(s)	368	94·6
Upsets of micturition	173	44·5
Paraesthesiae	135	34·7
Diplopia	84	21·6
Dimness or loss of vision	57	14·7
Vertigo	32	8·2
Facial paralysis	12	3·1
Pain in legs	11	2·8
Pain in back	10	2·6
General debility	10	2·6
Headache	8	2·1
Disorder of speech	6	1·5
Loss of sensation over one side of face	4	1·0
Vomiting	3	0·8
Deafness	3	0·8
Epileptiform attacks	2	0·5
Difficulty in swallowing	2	0·5
Mental confusion	1	0·3

Examination of the Patient

It would be reasonable to suppose that, in the early phases of disseminated sclerosis, signs which by custom we speak of as being "organic" are minimal. As previously emphasized, however, these signs are in reality evidence of disturbed function and not of structural change. Thus even in the earliest stages of disseminated sclerosis signs occur which are of fundamental importance in differentiating the disease from hysteria. This difficulty in distinguishing early disseminated sclerosis from hysteria was stressed by Buzzard (1897) in the following words: "In its infancy . . . the name given to disseminated sclerosis is hysteria." Further, it must be remembered that in all the phases of disseminated sclerosis hysterical manifestations complicate the clinical picture. Brain (1930) has observed that hysterical symptoms occur more often with disseminated sclerosis than with other organic diseases of the nervous system.

The physical findings which will be referred to are largely based on the result of examination of cases in the hospital series. The majority of these patients were in the oligosymptomatic stage of disseminated sclerosis. We are of the opinion that these signs occur and are of equal significance in the earlier phase of the disease.

1. Mental State of the Patient

The frequent hysterical overlay in cases of disseminated sclerosis has already been mentioned. Cottrell and Wilson (1926) stressed as being of diagnostic importance the triad of change in prevailing emotional disposition, change in emotional expression and control, and change in sense of physical well-being. Since available records were inadequate, no statistical analysis of this aspect was undertaken. Our impressions, however, are in accordance with the conclusions of these authors.

2. Neurovascular Phenomena

Vasomotor symptoms are common in patients with disseminated sclerosis. Thus cold hands and feet, acroparaesthesiae, and chilblains are often encountered. Erythromelalgia occurred in one case. Purves-Stewart (1945) observes that this condition may be one of the earliest signs of organic spinal cord disease such as disseminated sclerosis.

We have been impressed by the fact that weakness in a limb is often associated with a lowered skin temperature in that limb. It is possible that cutaneous angioneurosis may be an expression of "the soil" which predisposed to the development of disseminated sclerosis. Vasomotor instability of the extremities in disseminated sclerosis has also been referred to by Langworthy (1948).

3. The Eyes

We have found that three ocular signs have an important diagnostic value in disseminated sclerosis. This triad consists of imbalance of the ocular muscles, mydriasis, and hippus.

The ocular imbalance does not amount to strabismus, which in our experience is infrequent; it rather suggests a somewhat dissociated action of the extrinsic muscles of the eyes.

The pupils are generally larger than the average. In only five cases (6.3%) of the hospital series were the pupils myotic. Associated with this is the fact that the pupils are unduly mobile. The reaction to light is generally brisk. In only two cases (2.5%) was the light reflex absent. Similarly, the reaction of the pupil to near vision was found to be brisk in 74 cases (93.7%). The occasional occurrence of paralysis of accommodation has been referred to by Kinnier Wilson (1940), and was observed in three cases (3.8%) of the hospital series. In no instance were the requirements of the Argyll Robertson pupil fulfilled.

In a considerable number of cases the phenomenon of hippus was observed. Lagrange and Marquezy (1924) have referred to the occurrence of hippus in disseminated sclerosis, but it is felt that its presence is not accorded enough importance in textbooks or in teaching.

Gowers emphasized the difficulty in distinguishing between cases of disseminated sclerosis and neurosyphilis. We would suggest that the association of ocular imbalance, mydriasis, and hippus in disseminated sclerosis is of considerable importance in the differential diagnosis of these two conditions. With regard to other ocular manifestations, the pupils are not infrequently unequal and sometimes irregular. Nystagmus occurred alone or in combination with other components of Charcot's triad in 38 (47.9%) of the 79 hospital cases. The "characteristic" ophthalmoscopic picture is that of pathological pallor of the temporal half of the optic-nerve head. Such was found in only 13 (16.5%) of the hospital series. This figure is very low compared with that of "over 50%" suggested by Brain (1947). It closely approximates, however, to the incidence of symptoms referable to retrobulbar neuritis which occurred in 13.9% of the total series as a first symptom. Further, it is our experience, as it was of Adie (1932), that retrobulbar neuritis occurs relatively infrequently after the disease is established. In our series pathological temporal pallor of the optic disk was not present in a high proportion of cases; the absence of this feature should in no way cast doubt on this diagnosis.

4. Knee-jerks

Of the various tendon reflexes, particular diagnostic importance attaches to the knee-jerks. These were regarded as normal in only 7 (8.9%) of the 79 hospital cases. The knee-jerks were unequal in 36 patients (45.5%). In no patient in this series were these reflexes abolished.

5. Abdominal Skin Reflexes

In the diagnosis of disseminated sclerosis the importance of the abdominal skin reflexes is evident from the fact that they were abnormal in 77 patients (97.4%) in the hospital series. They were present normally in only two instances. In 69 cases (87.3%) there was bilateral loss of the reflex; in three (3.8%) unilateral loss was reported, and in five (6.3%) the abdominal reflexes were regarded as being readily exhausted.

The importance of the absent abdominal reflex was noted by Risien Russell (1910). Strümpell is quoted by him as finding them absent in 67% of 24 cases of disseminated sclerosis, compared with 13.5% in 185 persons with normal nervous systems. In Probst's series, quoted by Russell, the abdominal reflex was absent in 73% of cases. "The almost constant absence" of this reflex was emphasized by Adams (1921). Kinnier Wilson (1940) considered that suspicion of disseminated sclerosis should be attached to a case in which the abdominal reflex can be tired. Similarly, Purves-Stewart (1945) stresses the significance of absence or diminution of the reflex on one or both sides. Further, we would suggest that disseminated sclerosis should be suspected in a young patient whose abdominal reflexes do not share in the overactivity of the knee-jerks, should this latter abnormality be present.

Böhmig (1922), analysing 155 cases, considered that the addition of any single nervous physical sign to the combination of spastic phenomena in the lower limbs and the loss of the abdominal reflexes justifies the diagnosis of disseminated sclerosis, syphilis being excluded. This view is undoubtedly correct. It is emphasized, however, that spastic phenomena in the legs are not essential to the diagnosis. In a young adult the presence of a sign or symptom referable to a lesion in the white matter, associated with any of the abnormalities of the abdominal skin reflex mentioned above, should arouse suspicion of disseminated sclerosis. Wartenberg (1944) considers that the abdominal muscle reflex was of value in detecting a pyramidal-tract lesion "much earlier, better, and more surely" than the loss of the abdominal skin reflex. Such a view may be acceptable if significance be restricted to the loss of the skin reflex. If, however, the importance of the other abnormalities of the skin reflex be appreciated, it is felt that in disseminated sclerosis, at any rate, this reflex is at least of equal value in the early recognition of disturbed pyramidal-tract function.

The abdominal skin reflex was abnormal in several instances in which the plantar response was either equivocal or flexor. On the other hand, in no instance was an extensor plantar response associated with normal abdominal skin reflexes. An extensor plantar response (Babinski phenomenon) occurred in 66 cases (83.5%), in 8 (10.1%) it was equivocal, and in 5 (6.3%) it was flexor. In several instances Chaddock's sign has furnished evidence of pyramidal-tract dysfunction at a stage in which the plantar response was flexor or equivocal.

6. Adductor Spasm

We have found hypertonus of the adductor muscles of the legs to be the earliest manifestation of spastic phenomena in the lower limbs. As such, by constituting one of Böhmig's criteria, it is of value in the diagnosis of disseminated sclerosis.

7. Sensory Phenomena

The presence of signs referable to dysfunction of the posterior columns occurred in 37 cases (46.8%) of the hospital series. In this connexion, impairment of vibration sensibility was found to be the earliest manifestation of dorsal cord involvement. Loss of spinothalamic-tract function was unusual, and was found in only three patients (3.8%).

Summary

The symptoms and signs of 389 cases of disseminated sclerosis are discussed.

Weakness in one or more limbs was the first symptom in more than half the cases examined, while visual upset was the earliest manifestation in a further 26% of the patients.

The onset of the disease was found generally to occur in the age group 20–45 years, and when disseminated sclerosis is suspected in patients outside these limits other aetiological factors should be carefully considered.

For the development of disseminated sclerosis personal susceptibility is of importance, and in our experience the incidence of the disease is greatest in those with a sympatheticotonic diathesis.

Reference is made to those clinical signs which are of importance in distinguishing disseminated sclerosis from the manifestations of hysteria. In this connexion significance should be attached to the association of overactive knee-jerks and sluggish or readily exhausted abdominal skin reflexes. Other signs of diagnostic value are the mental state of the patient, the presence of neurovascular phenomena, and the triad of ocular imbalance, mydriasis, and hippus.

Stress is laid on the need for recognition of the disease before permanent damage has been inflicted on the central nervous system. Whatever advances in treatment the future may hold, the degree of recovery will depend on the stage at which a diagnosis is first established.

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AFTER-HISTORY OF SUCCESSFULLY TREATED CASES OF SUBACUTE BACTERIAL ENDOCARDITIS

BY

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The outstanding achievement of penicillin in overcoming infection in subacute bacterial endocarditis and in procuring a 65% cure (Christie, 1948) has presented new problems in prognosis. The immediate prognosis has received much attention, and an evaluation of the facts on which it may be based has often been presented (Jones *et al.*, 1947; Christie, 1946, 1948, 1949). The long-term influence of the infective process on the heart has naturally not received equal attention owing to the relatively short time since successful treatment of the infection was initiated. As penicillin has now been available for the treatment of subacute bacterial endocarditis since 1944 in America and since 1945 in this country, sufficient cases have been followed over a period of years for a tentative expression of remote prognosis to be offered.

Prognosis in rheumatic heart disease itself is always difficult owing to the tendency to additional damage due to relapse or reinfection, *ouvert* or subclinical. When it is appreciated, as Matthew and Gilchrist (1949) and MacIlwaine (1947) have shown, that the bacterial infection is frequently engrafted on a heart the seat of concomitant active rheumatic carditis, the difficulties of the assessment of the prognosis in subacute bacterial endocarditis will be seen to be further increased. Therefore prognostication of the after-effects of a bacterial infection engrafted on such a background cannot be easy, nor is it likely to be accurate. Deterioration will be difficult to ascribe either to the natural trend of the original rheumatic infection (DeGraff and Lingg, 1935) or the occurrence of rheumatic relapse, or to the after-effects of successful penicillin therapy for the superimposed bacterial infection. Despite such difficulties, it is important to know the fate of survivors from a disease which up to six years ago carried a 96% mortality (Lichtman, 1943).

Of a total of over 40 patients treated for subacute bacterial endocarditis, 20 have been cured for 27 months or longer. These 20 unselected patients provide the information on which assessment of remote prognosis is based. These patients have been closely followed up for periods varying from 2¼ to 5¼ years. Since discharge from hospital no survivor has relapsed or become reinfected, although at least one has had a further attack of rheumatic fever. The absence of relapse or reinfection is noteworthy, as Christie (1949) has indicated that the incidence of delayed relapse is of the order of 2% per annum.

A severe infection of the endocardium and myocardium, often of six months' duration before being arrested, is likely to lead to further cardiac damage. Apportioning of the degree of damage by the bacterial infection, in a heart already the seat of rheumatic or congenital pathology, is difficult for the reasons already advanced. Deterioration, if noted, cannot invariably be ascribed to the healing of the bacterial infection, as the relentless progress of the underlying rheumatic lesion will, especially in the elderly patient, contribute to a greater or less extent.

The cardiac efficiency of successfully treated cases can best be assessed by a study of three factors: (1) a comparison of the patient's capacity for effort before infection and after recovery; (2) changes in the heart size as noted

radiologically; (3) the detection of physical signs indicative of new valvular lesions or an increase in the severity of established lesions.

Exercise Tolerance

Table I shows the comparison of cardiac grade (New York Heart Association, 1939) before and 2¼ to 5¼ years after treatment. The preponderance of cases with good exercise tolerance before acquiring infection is in accordance with the findings of Libman and Friedberg (1948) that subacute bacterial endocarditis rarely occurs in the presence of advanced rheumatic heart disease. The information in Table I is revealing. Of 11 cases in Grade 1 (symptom-free before treatment) only one has shown deterioration in capacity for exertion, and that only to a slight extent. In seven patients classified as Grade 2a before the bacterial infection was acquired no deterioration was observed with the passage of the years.

TABLE I.—*The Cardiac Grade Before and After Treatment*

Cardiac Grade	Before Infection	After Infection	Died
1	11*	11†	—
2a	7	7*	1
2b	2†	0	—
3	0	1	—

* One deterioration. † One improvement (congenital heart).

One patient with congenital pulmonary stenosis was convinced that his exercise tolerance had improved considerably subsequent to the infection. In one patient, aged 34, classified as Grade 2b, further deterioration has become manifest by advancement into Grade 3 (congestive heart failure).

There has thus been a remarkable maintenance of capacity for effort in the survivors. All but two patients have resumed their former occupations or are now undertaking employment as strenuous as that prior to the onset of the infection. Of the two patients not working, one developed a right-sided hemiplegia during treatment and, although employable, has not yet been suitably placed; the other, in Grade 3, is naturally unfit for work. The occupations of the survivors range from busy housewife to general labourer, farm-worker, electrician and shop-assistant.

Four female patients have married since their illness, two have borne children without difficulty, and one is healthy at the sixth month of pregnancy at the time of review.

The degree to which subjective evidence of increased myocardial damage is absent is remarkable. Investigation of the second factor of assessment—*x*-ray examination for alteration in heart size—tends to substantiate the subjective evidence of lack of permanent damage from the infective process.

Heart Size

X-ray records were available of the size of the heart in two instances shortly before the onset of infection. In the remaining cases the heart size was assessed in the postero-anterior and both oblique views, if possible during the first week in hospital. This latter time of examination naturally varied with the duration of infection before admission. The variation, however, does not appear to confuse the deductions that can be made.

All patients had radiographs taken at the time of their follow-up, and the heart size was compared with that before or early in the infection (Table II).

The grades of heart size employed are: normal; slight enlargement, for a heart having one or more chambers just outside the limits of normal; one "plus" for a heart definitely enlarged in one or more chambers; and two "plusses" for a grossly enlarged heart. In only four instances did the heart enlarge during or after subsidence of the infection. No heart which was normal in size before treatment subsequently enlarged; increase, if it did occur, took place in a heart already enlarged to some degree.

TABLE II.—*Change in Size of Heart Found at Follow-up. In Only Four Instances has the Heart Enlarged*

Heart Size	Before or Early in Infection	At Follow-up			
		Normal	Slight	+	++
Normal	5	5			
Slight enlargement ..	10		8	1	1
+	5			3	2

Investigation of the four cases with evidence of change in heart size shows that the enlargement has not been slowly progressive over the years since cure. It occurred to its greatest extent during the weeks of penicillin treatment, and thereafter the size has remained almost stationary. It may be noted in passing that in no instances did the heart enlarge during treatment, only to regress during convalescence—a finding contrary to that of Jones *et al.* (1947), who report three cases showing enlargement which subsequently lessened, although only to a very slight extent. It is therefore assumed that, should the heart enlarge during treatment, it is likely to remain enlarged. That cardiac enlargement during the process of eradication of infection is the result of the bacterial infection cannot be certain. A concomitant rheumatic infection might as readily produce such a change in size.

Further investigation of the four cases with an increase in size shows no constant feature such as age, rhythm, valvular lesions, length of time prior to treatment, past or present rheumatic history, or electrocardiographic evidence of myocardial damage sustained during the bacterial infection, any of which might be responsible for the increase in size. Nor does the increase in heart size correlate with any deterioration in exercise tolerance except in one of the four cases—the patient formerly in Grade 2b and now in Grade 3 has considerable enlargement of the left ventricle and auricle. Jones *et al.* (1947) found that cardiac enlargement occurring at the time of, or subsequent to, treatment was usually associated with decreasing capacity for effort. There is therefore no doubt that heart size on termination of treatment is an important observation in assessment of remote prognosis. Although deterioration may not be evident, it is to be expected that the larger heart will fail earlier.

Fresh Valvular Damage

The finding of fresh evidence of valvular lesions in a heart the seat of rheumatic pathology cannot be ascribed solely to the bacterial infection and the healing process. However, Rosenblatt and Loewe (1945) and Bloomfield *et al.* (1945) have demonstrated cases in which the mutilation of the valves immediately after penicillin therapy has been such as to constitute a grave mechanical handicap and to contribute materially to heart failure. In a series of fatal cases (Matthew and Gilchrist, 1949) no such destruction was evident at necropsy in 13 instances, except that in one case an aortic cusp had perforated as the result of the infection.

A comparison of the auscultatory findings at the outset of treatment and at the time of follow-up is presented in

TABLE III.—*Valvular Lesion Before and After Treatment. The Term "Mitral" is Employed to Cover Mitral Stenosis and Mitral Damage*

Valvular Lesion	Before Treatment	After Treatment
Mitral	9	8
Aortic incompetence and mitral	7	8
Aortic stenosis	1	Died
Congenital	3	3

Table III. In only one instance is there now evidence of additional valvular damage, aortic incompetence having appeared where previously mitral stenosis was the sole lesion. In three other patients the heart murmurs have permanently altered in character. This finding suggests that in these four instances it is probable that the healing of the infective process had some effect on the structure of the valve cusps.

Arrhythmias

Once again it must be emphasized that an alteration in rhythm cannot be attributed with any degree of certainty to the effects of the bacterial infection. However, three patients now suffer from occasional attacks of palpitation which have been shown by electrocardiogram to be due to paroxysmal auricular fibrillation. One additional patient has developed frequent ventricular extrasystoles. These arrhythmias do not disturb the patients unduly, but in one instance the cardiac grade has deteriorated to Grade 2a.

One Death

One patient died 29 months after treatment. He was 49 years old and was the only case of pure aortic stenosis in the series. He gave no rheumatic history, nor was there an aortic diastolic murmur or evidence of rheumatic heart disease, thus suggesting that he comes into the category of pure aortic stenosis (Kiloh, 1950). Death occurred from congestive heart failure of rapid onset and increasing in severity over the course of two months. There was no suspicion of reinfection or relapse of the bacterial infection, nor was there subjective evidence of active rheumatism. Details of his last illness when correlated with a history of effort pain for two years prior to acquiring the bacterial infection indicated death from congestive heart failure subsequent to ischaemic myocardial damage. As death occurred in the patient's home in the north of Scotland a post-mortem examination was not made.

Discussion

The significant prognostic features affecting the immediate outcome of a case of subacute bacterial endocarditis have been clearly enunciated (Jones *et al.*, 1947; Christie, 1948; Bramwell, 1948; Matthew and Gilchrist, 1949). Sufficient time has now elapsed since the availability of penicillin to suggest features of significance pertinent to the remote prognosis of this disease. The period since treatment does not permit of dogmatic statement, but points are now evident which, observed at the time of cure of the initial infection and subsequently, allow a tentative opinion to be expressed.

This disease, carrying in 1943 a 96% mortality rate (Lichtman, 1943), has had the immediate mortality rate reduced to around 30% (Wagner, 1948). Penicillin can unstintingly be credited with this remarkable improvement. As 25% of cases sustain myocardial damage of some magnitude during the infection (Seabury, 1947), it might be assumed that antibiotic therapy, in overcoming the infection, would leave the patient a cardiac cripple. That this does not pertain is amply demonstrated by a study of this series of 20 cases followed for 27 to 63 months. Apart from one death, deterioration in capacity for effort has been restricted to two instances; ten patients remain in cardiac Grade 1 before and after infection and six maintain a grading of 2a despite the infection.

Other investigators have had less encouraging results in the subsequent progress of their cases and have endeavoured to explain on various grounds the deterioration and, on occasion, death of their patients long after eradication of the infection. Kaplan *et al.* (1949), in a study of 18 cases followed up from 25 to 61 months after the infection was cured, found that in 12 instances the infection had behaved as an intercurrent process, the healing in no way aggravating the pre-existing heart disease. Of the remaining six cases, three had a greatly reduced exercise tolerance and three died of congestive heart failure. The severity of the underlying rheumatic infection might have brought about such developments; however, no information is given regarding the age, cardiac grade, or rhythm which might assist in determining this point. One factor common to these six cases and not noted in any survivor is that all had a high pulse pressure on termination of treatment or shortly afterwards. In five this was due to a severe degree of aortic incompetence and in the sixth to a patent ductus arteriosus.

Kaplan postulates that the healing of the infected valve under the influence of penicillin may induce a severer degree of aortic incompetence than would occur in the natural process of the rheumatic endocarditis. Rosenblatt and Loewe (1945) were early aware of this possibility. Kaplan emphasizes that the degree of aortic leak must be sufficient to cause a "dynamic" burden on the heart mechanism. In the series under consideration the one patient who died suffered from aortic stenosis and had no aortic regurgitation. He did, however, suffer from myocardial ischaemia.

Seven cases in this series had aortic regurgitation (Table III). In three the diastolic pressure shortly after the completion of penicillin therapy was below 60 mm. Hg and has since remained below that level. This could be considered as imposing a "dynamic" burden on the myocardium. None of these seven cases shows any deterioration in exercise tolerance. One patient, who had only an organic mitral systolic murmur at the end of treatment, now also has aortic regurgitation with a blood pressure of 134/60. Her cardiac grade has deteriorated from Grade 1 to Grade 2a. She also suffers from paroxysmal auricular fibrillation. Rapoport and Ellis (1948) report 11 cases studied two years after successful penicillin treatment. No deterioration occurred in the four cases of their series showing aortic valve involvement. The degree of valvular damage is not, however, stated. In fact, all 11 of their cases were "at least as well and as active, and some could do more," as compared with their condition before the bacterial infection.

Bramwell (1948) is inclined to vest the healing process under the influence of penicillin, at least in the instance of the mitral valve, with diagrammatically opposite powers to those of erosion and destruction. On the evidence of one patient who originally had aortic incompetence at the time of infection and who two years later developed mitral stenosis, and on the fact that in two other patients the electrocardiograph showed an increased tendency to right axis deviation, it was postulated that, in the process of healing, a stenotic lesion may develop or increase in severity at the mitral valve. The three cases mentioned were the only instances in which deterioration in exercise tolerance occurred in the 18 patients reported on two years after eradication of infection.

In my series no patient developed a stenotic valvular lesion, nor did stenosis once present tend to increase,

although the patient dying of aortic stenosis may have been in this category. The alteration in the pitch of the mitral systolic murmur observed in three patients is not necessarily indicative of incipient stenosis. The development of right axis deviation can be attributed to the natural progress of rheumatic heart disease without evoking the healing process of the bacterial infection even as a contributory factor. Based on the slender evidence of one case in this series and another in which the infection has not been eradicated long enough, the effect of the healing process, at least on the pulmonary valve, seems to be the opposite of a stenosing tendency.

A boy aged 14 suffering from congenital pulmonary stenosis with superimposed subacute bacterial endocarditis was unable to trot the length of a football pitch before infection. Now, four years after infection, he can partake energetically in a game of football without undue breathlessness. This improvement cannot be the result of the natural evolution of pure pulmonary stenosis, the tendency in such cases being relentless deterioration (Allanby and Campbell, 1949). It would appear that the infection had freed the stenosis after the nature of a Brock (1948) operation. The other patient with infection eradicated from a stenosed pulmonary valve or infundibulum possesses a capacity for effort greater than she has enjoyed for years. Neither patient has a pulmonary diastolic murmur, only a systolic thrill and murmur at the base of the heart with conclusive *x*-ray and electrocardiographic evidence of the diagnosis. This evidence that healing of the infected process possesses destructive rather than fibrotic powers in the instance of the pulmonary valve has been noted by Pollack *et al.* (1948). As has already been shown, at least in this series, a similar development has fortunately not occurred in healing aortic valves.

Conclusions

In the vast majority of cases of subacute bacterial endocarditis it would appear that, provided the infection is overcome and congestive heart failure avoided at the time of treatment and shortly afterwards, the disease can be regarded as an incident which leaves little or no evidence of additional permanent damage in a heart the seat of congenital or rheumatic disease. In the few cases in which deterioration occurs, it may be anticipated if attention be paid to the following facts : the cardiac grade of the patient when the infection is acquired ; the detection of a severe degree of aortic regurgitation after elimination of infection ; and the heart size, radiologically, during and immediately after eradication of infection.

Summary

Twenty cases of healed subacute bacterial endocarditis have been followed for periods of between 27 and 63 months. No case relapsed or became reinfected after successful treatment of the bacterial infection. One death occurred.

The effect of the bacterial infection in two cases of congenital pulmonary stenosis is described.

The exercise tolerance, radiological heart-size, and auscultatory features at the time of treatment and after the lapse of years are compared and the significant points identified.

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CONGENITAL MALARIA

REPORT OF THREE CASES

BY

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A considerable divergence of opinion persists regarding the frequency with which congenital malaria may occur. That it is occasionally encountered there can remain no doubt. Jones and Brown (1924) reported two authentic cases in London, while cases have also been recorded by Beekel (1910), who describes 12 instances of undoubted placental transmission, by Tanner and Hewlett (1935), and by Van Nitsen (1932), who demonstrated malarial schizonts in the spleens of six infants, either born dead or dying soon after birth. Chen *et al.* (1944) have summarized 39 cases of congenital malaria from the world literature, while Wickramasuriya (1935) believes that transplacental foetal infection occurs more often than is normally conceded and records six proved cases of *Plasmodium falciparum* infection.

Most British and American authors, however, while recognizing the possibility of congenitally transmitted malaria, regard its occurrence as a rarity. Thus English (1946), who was in charge of a large maternity hospital in Singapore for 20 years, encountered only one case of congenital malaria amongst the 5,551 deliveries during 1938—a European infant aged 6 days.

During and since the recent war many European women have elected to produce their babies in Nigerian hospitals, and the possibility of congenital malaria has become a significant consideration. Since congenital transmission is still generally regarded as a remote contingency, a pyrexial illness in the first few days of life is more likely to raise suspicions of neonatal infection, while a convulsive seizure will more probably suggest an intracranial birth injury. Even less likely is the possibility of congenital malaria to be entertained in the cases of such women who return to the United Kingdom to have their babies. Therefore three cases personally encountered are recorded.

Most non-African labours in Lagos are conducted at the Creek Hospital, the patients being mainly Europeans, Syrians, or Lebanese of varying duration of residence in the country, though almost all may be assumed to have been subject to subtertian malaria at one time or another.

The occurrence of three confirmed cases of congenital malaria during February, 1949, suggested the possibility that certain of the neonatal deaths in earlier years might have been similarly caused. An investigation of the records, however, showed that of the four deaths occurring within the first 12 days of life in the course of the 143 deliveries conducted during 1947 and 1948 only one could possibly be attributed to congenital malaria. From January 1 to June 30, 1949, the period under consideration, there were 37 accouchements.

Case 1

An Englishwoman aged 29 had been resident in East Africa for some years, and was subject to periodic malarial attacks. She had arrived in Nigeria about one year previously, had taken suppressive quinine somewhat irregularly, but since arrival had had no overt attack of malaria. Her husband was English. She had two children, aged 6 and 4 years, her first labour having been prolonged and followed by subinvolution, the second being easy and normal. Throughout the present pregnancy she had been well, with the exception of one attack of cystitis. Her expected date was February 1, and she was admitted at 4.30 a.m. on February 11 with good pains, os dilated two fingerbreadths, a persistent occipito-posterior presentation, and premature rupture of the membranes. At 7.30 a.m. she was easily delivered of a healthy female infant. The maternal blood on admission showed no malaria parasites.

The infant remained quite well till February 13, when it was observed to be fretful and to be vomiting after feeds. At 2 p.m. that day the rectal temperature was 102.6° F. (39.2° C.); the mouth was healthy, the cord was clean, and the chest, cardiovascular system, and abdomen showed no abnormality, but the vulva appeared slightly inflamed, with a scanty thin purulent discharge. A blood smear was taken, and 5,000 units of penicillin intramuscularly three-hourly and 0.125 g. of sulphathiazole six-hourly were prescribed.

At 10 a.m. next day the blood smear was reported to contain scanty subtertian rings, and 2 gr. (0.13 g.) of quinine was given intramuscularly, and 1 gr. (65 mg.) of quinine orally three times a day was prescribed. At 4.30 p.m. the infant was very ill, with a poor slaty colour. At 6.30 p.m. there was a slight improvement; the spleen was found to be palpable and a further 2 gr. of quinine was given intramuscularly. At 9 p.m there were continuous convulsions and the condition was very poor. The infant, whose temperature was now 105° F. (40.6° C.), was sponged with tepid water, and 3 min. (0.18 ml.) of syrup of chloral was given, this being repeated at 9.30 p.m. At 11 p.m. convulsions had ceased, but diffuse moist rales were heard in the lungs: atropine, 1/600 gr. (0.11 mg.), was given and oxygen administered by oral catheter.

At 12.30 a.m. on February 15 the infant was asleep; the respirations were, however, irregular, and there appeared to be a one-in-three heart-block. At 8.30 a.m. she was quiet, the pulse and respirations were regular, but the temperature, which had been sustained, was 104.4° F. (40.2° C.), and 2 gr. of quinine was given intramuscularly. At 9 a.m. there was renewed respiratory and circulatory depression with cyanosis and occasional twitching of the upper limbs, and death occurred half an hour later. Necropsy was not performed.

Case 2

The mother, aged 37, and her husband were Europeans of French nationality. She had been resident in Nigeria for many years, and had had numerous bouts of malaria, though none recently, but took suppressive proguanil, 100 mg. daily. She had three children, the youngest aged 2½ years, and had had no miscarriages. All previous labours had occurred two or three weeks before the expected date, and all had been easy and rapid. She had been well throughout the present pregnancy and the expected date was March 4. Pains started at 5 a.m. on February 20. She was admitted at 6.30 a.m., and an easy rapid vertex delivery was completed by 7 a.m. The maternal blood showed no malaria parasites.

The infant, a healthy female, was bottle-fed from birth. The cord-blood smear, taken at birth, contained scanty subtertian rings, and ½ gr. (32 mg.) of quinine orally three times a day was prescribed from birth.

At 2 p.m. on February 23 the baby appeared unwell and was vomiting. The rectal temperature was 101° F. (38.3° C.). At 11.15 p.m. 2 gr. of quinine was given intramuscularly. At midnight the vomiting was more severe; it was accompanied by hiccup, a slaty cyanosis, and some twitching of the arms and eyes.

At 1.15 a.m. the next day 3 min. of syrup of chloral was given. At 8.30 a.m. the condition had somewhat improved. The cord was separated cleanly, the chest and cardiovascular system showed no abnormality, but the liver edge was palpable and there was slight icterus. Quinine, 1½ gr. (0.1 g.), was given intramuscularly. At 3.45 p.m. the temperature was 102.8° F. (39.3° C.), the jaundice was deeper, the liver was enlarged to one fingerbreadth below the costal margin, and there were diffuse bilateral moist rales. Penicillin, 5,000 units intramuscularly three-hourly, was prescribed, but death occurred at 5 p.m. Permission for a full necropsy was not obtained, but a post-mortem hepatic puncture smear showed scanty malaria parasites.

Case 3

A Scotswoman aged 29, the wife of an African, had been resident in Nigeria for one year only and took daily suppressive quinine. She had two children, aged 3 years and 1 year 8 months, both labours having been easy, and had had no miscarriage. She had been well throughout the present pregnancy apart from an attack of malaria three weeks before delivery, when she was treated with 0.1 g. of mepacrine orally thrice daily for one week. Her expected date was March 4. She was admitted at 11.15 p.m. on February 25, and an easy vertex labour was completed one hour later. Her blood on admission showed no parasites, but from February 27 to March 1 she had slight pyrexia (99 to 99.8° F.—37.2 to 37.7° C.) accompanied by headache, which responded to a further course of oral mepacrine.

The infant was a healthy half-caste male, and the cord blood at birth contained scanty subtertian rings. On the day of birth, February 26, 3 gr. (0.2 g.) of quinine was given intramuscularly, and ½ gr. thrice daily by mouth and proguanil, 25 mg. twice daily, were prescribed. Next day a further 3 gr. of quinine was given intramuscularly. On the 28th there was slight pyrexia, but the infant seemed to be well and was taking his feeds. The chest, abdomen, and cardiovascular system were normal, and the blood showed no malaria parasites. There was slight swelling of the left buttock, probably post-injection. Another 3 gr. of quinine was given intramuscularly. At 4.30 p.m. the baby was unwell, with slaty colour and vomiting, and 2 gr. of quinine was given intramuscularly. On March 1 there was rapid deterioration, with coffee-ground vomits, and death occurred at 5.30 a.m. Necropsy was not carried out.

Subsequent to Case 1 every expectant mother was prescribed, in addition to her customary daily suppressive, 400 mg. of proguanil daily, beginning 10 days before the expected date and continuing until admission in labour; a cord-blood smear was also taken at every birth and examined for malaria parasites. Of the 37 deliveries, the first six were not cord-tested: the 31 which occurred after Case 1 were all cord-tested at birth, and only Cases 2 and 3 showed positive smears. Placental smears were not examined as a routine, as it was felt that the universal daily suppressive habit would certainly invalidate the results.

Since my departure from the Creek Hospital there have been a further 23 deliveries during July and August, 1949, all infants being cord-tested at birth. Of these only one showed parasites in the cord blood: a febrile illness developed within a few days of birth, but responded to treatment. A second infant, despite a negative cord blood, developed high pyrexia 26 hours after birth, and was tentatively diagnosed on clinical grounds and therapeutic response as a case of malaria.

Discussion and Conclusions

Since the initial case of congenital malaria, three cord bloods in the course of the next 54 deliveries showed subtertian rings, and all three infants subsequently developed symptoms compatible with a diagnosis of malaria. Of the 51 infants whose cord blood smears were negative, only one developed suggestive symptoms. It is concluded that among non-indigenous European women of relatively low immunity, infected with the Lagos strain of *P. falciparum*, congenital transmission of malaria is by no means rare.

As regards predisposing causes, only one of the three mothers admitted to any recent malarial attack, so that placental transmission may occur in the absence of any overt maternal malarial bout during pregnancy. In all three cases the placenta was macroscopically healthy and intact, an observation which does not support Manson-Bahr's (1940) hypothesis that transmission to the foetus can occur only through a placental breach or defect.

There seem to be few effective precautionary or preventive measures. Thus regular suppressive procedures throughout pregnancy, here almost universal, did not seem to give reliable protection; nor, indeed, did a therapeutic course of proguanil, and in one case mepacrine, before delivery. It is, however, strongly urged that in the case of West Coast wives, whether delivered there or in the United Kingdom, the cord blood should be examined at birth as a routine.

Among the salient clinical features in these three cases was the fact that all three mothers were multiparous and past their first youth, being aged 29–37 years. Two had been long resident in the Tropics and previously subject to malaria, though admitting of no recent attack; while the third, a more recent arrival, had suffered an attack of clinical malaria three weeks before delivery. All labours were easy and rapid.

The intervals between birth, when the infants appeared healthy, and the onset of symptoms were 54, 77, and 60 hours, suggesting the possibility of a short-lived passive protection due to maternal antibodies. The earliest manifestations were pyrexia, vomiting of feeds, and a poor colour—a slaty pallor. Convulsions supervened later, and finally pulmonary oedema. One case exhibited hepatomegaly and jaundice, and one splenomegaly.

Quinine, intramuscularly and orally, in one instance combined with oral proguanil, proved quite ineffective. Subsequent experience of two cases of cerebral malaria in European infants under 6 weeks old suggests that intramuscular mepacrine is the treatment of choice and may be dramatically effective. In each case an intramuscular injection of 0.1 g. of mepacrine precipitated an alarming convulsive seizure within 15 to 20 minutes, followed by complete recovery. To avoid this very real danger the dosage should be sufficiently small and divided—0.03 g. daily being suggested as adequate—and preferably begun immediately on discovery of a positive cord blood.

The notable contrast between hyperimmune indigenous populations, among whom placental infection is exceedingly common but congenital malaria very exceptional, and non-indigenous individuals of low immunity, among whom placental infection is very rare but congenital malaria relatively less so, cannot be passed without comment. In Sierra Leone, Blacklock and Gordon (1925) found placental infection in 38% of indigenous deliveries, but consistently failed to demonstrate parasites in foetal cord or peripheral blood, though Walton (1947), in Freetown, found 0.32% of 2,154 newborn infants to be congenitally infected. Bruce-Chwatt (1949—personal communication), in Lagos, reports a 26% placental infection rate in 450 African women but no single case of congenital malaria. Peel and Van Hoof (1948), from the Congo, record that of 400 African mothers 60% showed malarial infection; infection of the placenta was found in 53.9%, and yet no case of congenital malaria was encountered among the 393 newborn infants. In marked contrast, Clark (1915), in Panama, while finding a significant proportion of infected placentas in the West Indian negroes, found none among the European women.

It is suggested that with the increasing degree of immunity to malaria the frequency of infection of the placenta rises, while coincidentally the efficiency of the placenta as a barrier to foetal transmission increases and the incidence of congenital malaria falls.

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FATAL CASE OF POISONING DUE TO INHALATION OF METHYL BROMIDE

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Methyl bromide has been widely used of recent years in fire extinguishers for ships and aircraft, and in refrigeration plants. The dangers of exposure to this compound should therefore be better known than they are. For that reason we are reporting a fatal case with which we were concerned, and which arose from the scrapping of fire-extinguishers from aircraft engines.

Case Report

A man aged 21 was admitted to the Joint County (Fever) Hospital, Elgin, on December 2, 1947, at approximately 5 p.m. with a provisional diagnosis of meningitis. The history then available was that he had felt unwell at his work in the afternoon, had come home, had complained of headache, and quite suddenly at about 3.45 p.m. had had a convulsion, rapidly followed by others and by loss of consciousness. Subsequently it was learnt that the patient had been engaged on emptying and "cleaning" aircraft fire-extinguishers. The method employed was to perforate the lower end of the copper "bottle"—shaped like a vacuum flask—with a fireman's hatchet, and to let the vapour and fluid escape. Thereafter

the brass top was sawn off the bottle. Normally all this was done in the open air, but on the day in question there was severe frost, and the empty bottles were stacked in a shed and later cleaned there under cover. In the course of the morning's work, probably about noon, he had splashed a quantity of liquid methyl bromide over his clothes, a little of it reaching his face.

On examination the patient was having recurring convulsive seizures at the rate of about 10 a minute. These affected the jaw, back, both arms, and both legs, and were in the nature of clonic spasms. He was unconscious. An alcoholic odour in the breath was most pronounced. Attempts were made to control the spasms. Thiopentone was given, and, by adjusting the dose, control was effected for a few minutes at a time. During the first interval of freedom from spasm a further rapid examination was made, but there were no additional positive findings except that moist sounds were heard on auscultation of the chest. Samples of blood, urine, C.S.F., and stomach content were secured. The urine was blood-stained. A further dose of thiopentone at a later hour had the same effect. Between 10.30 and 11 p.m., after the intramuscular administration of paraldehyde had proved fruitless, 2 ml. of this drug was given intravenously, with 1/50 gr. (1.3 mg.) of atropine. This combination immediately controlled the seizures. In the course of the next few hours the general condition steadily deteriorated. Nikethamide was injected intravenously to combat respiratory depression, but large amounts counteracted the sedative action of the paraldehyde, leading to recurrence of the clonic spasms. The patient died at 5.15 a.m. on December 3.

At the necropsy on December 5 the stomach showed submucous haemorrhages at the distal end. The duodenum also showed submucous haemorrhages. The remainder of the bowel was normal. The liver, pancreas, and spleen showed no obvious changes. The chest cavity was normal in size; the pericardium was healthy; there was no evidence of valvular disease of the heart, and the heart muscle appeared healthy. The kidneys were very congested. The capsule stripped off easily; there was no evidence of inflammation of any duration, and the appearance of the cortex was in keeping with the condition of haematuria which developed on the night of the onset of illness. The brain showed no evidence of meningitis; the ventricles were normal; the surface of the brain was considerably congested and there were numerous small haemorrhages.

The appearances of the organs accorded with the absorption of an acute irritant poison which had caused submucous haemorrhages of the stomach and duodenum and had acted as a convulsant, causing congestion and haemorrhage of the cerebral cortex and acute congestion of the kidneys in the process of elimination.

Biochemical Findings.—Urine: a slight degree of albuminuria was found on direct examination; there were no other abnormal constituents. Blood: 30 mg. of NaBr per 100 ml. C.S.F.: No NaBr. Stomach contents: 30 mg. of NaBr per 100 ml. These findings suggest that a derivative of bromine was not the cause of death.

Discussion

Methyl bromide (CH_3Br) is a gas at normal temperatures, the boiling-point of the liquid being 4.5° C. (40.1° F.). It is a heavy gas, its weight being aproximately six and a half times that of air. Like chloroform, ethyl chloride, and carbon tetrachloride it is not inflammable. Its use as an agent for extinguishing fires depends on its weight, which leads to a blanketing effect and the exclusion of oxygen, or on its non-inflammability, which is utilized in aircraft engines, where it is played on the carburettor, thus lowering the flash-point of the petrol.

Poisoning by its agency was first noted in 1901, and up to 1940 a total of 42 cases had been reported in the literature. Of these, 12 were fatal, 23 recovered, and in the remaining 7 information was incomplete. From 1939 to 1944 an additional 22 cases were reported in the Royal Navy, with fatalities (Clarke *et al.*, 1945). Cases may have occurred among Air Force personnel, but under conditions of national emergency they would not be disclosed. Inquiry of R.A.F. medical personnel in the neighbourhood suggested that little was known of methyl bromide as a toxic agent.

Its mode of action depends largely on the concentration. If this is of the order of 10,000 parts per million the gas acts as a lung irritant. The victim seeks to escape, and if he does so the duration of exposure is unlikely to be sufficient to produce the chain of events described below. If he fails to escape, the signs, including post-mortem signs, are those of lung irritation, with haemorrhage and oedema of the lung and pleural effusion. Oxygen may be effective in treating this class of case.

If the concentration is in the neighbourhood of 1,000 parts per million the sequence described by Leschke (1934) is typical. After inhalation of the poison there are slight non-characteristic symptoms, such as headache, giddiness, fatigue, vomiting, and double vision. There is then a free interval of hours or even days, followed by the sudden onset of twitching, lockjaw, cramps, double vision, delirium, and raving madness. Leschke thinks that these symptoms are due to some intermediate metatoxic process, and not to the methyl bromide as such. In support of this view is the fact that methyl bromide has never been recovered from man or experimental animals. When death occurs in this class of case there has usually been some degree of pulmonary oedema and pleural effusion. Necrosis of the renal cortex is also a fairly constant sign. In only one other instance have we ascertained that haemorrhages into the cerebral cortex have occurred. This was one of a group of boys from an approved school who were living in a disused naval launch.

No curative treatment is known when convulsions have begun; indeed, in only one instance have we found a report of recovery after the onset of convulsions. Exposure to minimal concentrations of the order of 200–400 p.p.m. results in loss of appetite, nausea, headache, and muscular pains, the symptoms rapidly disappearing on cessation of exposure. Prolonged application of methyl bromide to the skin may lead to burning. It is clear, however, that this does not always happen, as workmen have used it to remove grease from their hands without ill effect. There is, in fact, a strong suggestion of idiosyncrasy.

One feature common to all the reported cases we have studied is its occurrence in an enclosed space, such as a ship, covered railway wagon, or workshop. In our case the actual opening was carried out in the open air, but the "cleaning" was done in a shed, and on a cold day. In our opinion this combination of circumstances led to imperfect emptying of the fire-extinguishers in the open air, with a consequent rise in the methyl bromide content of the shed to dangerous levels.

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THE INTERNAL SPERMATIC FASCIA

WITH REFERENCE TO REPAIR OF INDIRECT INGUINAL HERNIA

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The object of this communication is to stress the importance of a thorough exposure of the defect at the internal inguinal ring during the course of operation for repair of indirect inguinal hernia in adults. This step, which is usually dismissed all too briefly in descriptions of the operation, is an essential prerequisite to the performance of an accurate repair. A defect is always present in these cases but requires careful dissection to be clearly displayed, and it is obvious that unless this is done the repair can be only approximate and the risks of recurrence are thereby increased.

Hughes and Fathi (1948), in a short but clear and precise paper, have drawn attention to the same subject, but the manœuvre they advocate (see below) is not, in my experience, quite so easy as it sounds.

The operation referred to above is the one described, with slight modifications, by Ogilvie (1937), Edwards (1943), Lytle (1945), and others. On anatomical and pathological grounds it seems clearly to be the operation of choice. Its essential feature is the direct repair of the stretched internal ring after excision of the sac, without altering in any way the normal anatomy and mechanism of the inguinal canal.

But the difficulty is that the stretched ring is not immediately apparent; its margins are very indefinite and the transversalis fascia itself is not at all easy to identify. It is hoped to show that this difficulty can be overcome by the simple procedure to be described. At least I have found it extremely helpful in the course of some 200 operations.

Anatomy

It is necessary first to refer briefly to the anatomy of the internal inguinal ring. The ring is simply an opening in the transversalis fascia for the passage of the spermatic cord from the abdominal cavity into the inguinal canal. Lytle (1945) has shown that it is strengthened by an obliquely placed U-shaped fibrous sling over which the cord bends; but this is not really relevant to the present argument except to show that the normal ring has three well-defined margins—namely, superior, medial, and inferior—while the fourth one—that is, lateral or more precisely supero-lateral to the cord—is indefinite.

From the margins of the ring a tube of fascia—the internal spermatic fascia—is prolonged on to the cord, to which it closely adheres. In fact the cord does not pierce the transversalis fascia at all, but merely evaginates it at the internal ring (Fig. 1). The continuity of the internal spermatic fascia with the transversalis fascia makes it extremely difficult to decide what are the limits of the ring when viewed from the external aspect—that is, as seen at operation. *Gray's Anatomy* (1946) actually states: "This opening [the internal inguinal ring] is not visible externally since the transversalis fascia is prolonged on these structures [spermatic cord or round ligament] as the internal spermatic fascia." This observation can be easily verified on any normal subject in the post-mortem room and at every operation for inguinal hernia.

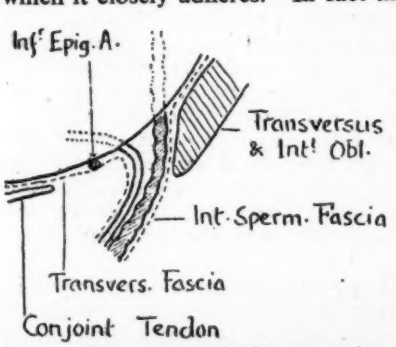

FIG. 1.—Diagrammatic horizontal section through the internal inguinal ring.

The Operation

When an indirect sac is present it is found to lie lateral and superficial to the cord, and always within the internal spermatic fascia. After the cord has been lifted out of its bed the fascial tube must be deliberately incised, and the sac may then be picked up with forceps and freed up to its neck by blunt dissection. It is excised as usual and the stump allowed to retract.

If the cord is now lifted up with slight traction and the conjoint tendon retracted outwards, the appearance will be more or less as shown diagrammatically in Fig. 2. The internal spermatic fascia will be seen to spread out funnel-wise as it approaches the internal ring, which at this stage is not visible. A rent is apparent in the fascia through which the sac was dissected, and is often reduced to a mere slit as the cord is lifted up. The stump of the sac will have disappeared within this rent. It is remarkable how this fascial tube, in spite of the rough treatment which it often receives during the dissection of the sac, becomes more or less accurately re-formed after the excision of the sac and maintains its attachments to the margins of the ring. Furthermore, the extent of the defect at the ring can be neither seen nor felt unless the finger is actually slipped through the rent just mentioned.

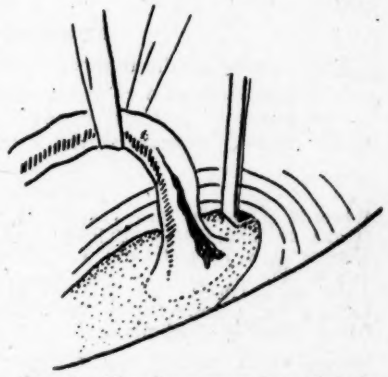

FIG. 2.—Showing appearance after the cord is lifted up with slight traction and the conjoint tendon is retracted outwards. The cremaster is omitted for the sake of clarity.

To expose the defect clearly and to display the margins of the ring, it is now necessary to divide the internal spermatic fascia all round the cord. It should be deliberately picked up with forceps and cut with scissors while gentle traction is exerted on the cord.

Slight difficulty may sometimes be experienced on the medial side of the cord, which is here tethered to the margin of the ring. The small cremasteric vessels are blamed for this by Hughes and Fathi. They stress the importance of these vessels, and state: "After the cremasteric vessels covered by their fascia have been exposed they are divided between silk ligatures. With the division of this 'ligament' the cord can be displaced laterally." However, I have never been able to expose them to my satisfaction, nor am I convinced that it is necessary to do so, because once the fascia has been divided the cord can be retracted laterally, and probably carries the vessels with it.

The stretched internal ring is now clearly displayed (Fig. 3), and usually admits the index finger easily. The cord is retracted laterally and the margins of the defect are approximated by interrupted sutures or a continuous suture medial to the cord. The newly reconstructed ring can in

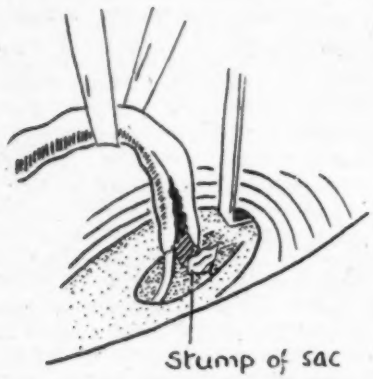

FIG. 3.—Showing the stretched internal ring.

fact be made as small as desired and should fit snugly round the cord.

In some cases the ring has been so stretched that its lower fascial margin is practically non-existent. In such cases the sutures may be anchored to Poupart's ligament inferiorly as described by Edwards, but even then it is usually possible with care to pick up with the needle a strand of tissue that will hold the stitches quite well just above Poupart's ligament and deep to the lower leaf of the cremaster.

Summary

The anatomy of the internal inguinal ring is reviewed.

The importance of a complete exposure of the stretched ring in operations for indirect inguinal hernia is stressed, and a simple method for ensuring this is described.

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Medical Memoranda

Parathion Poisoning

The increasing use of organic phosphorus insecticides has created a new occupational hazard to agricultural workers. Hunter (1950) has drawn attention to this group of compounds, which includes "parathion" (*para*-nitrophenyl-diethyl-thiophosphate), and has described casualties which have occurred elsewhere, although he noted that no cases of poisoning had been reported in Great Britain. Detailed information concerning organic phosphorus insecticides has been recorded by Goldblatt (1950), together with a description of the signs and symptoms of their toxic effects and the specific antidotal action of atropine. The case of parathion poisoning here recorded should serve to emphasize the nature of the risk, the importance of its prompt recognition, and the value of treatment with atropine.

CASE REPORT

A man aged 46 had been engaged for three weeks in preparing an insecticide spray for hops, using a commercial preparation containing 20% of parathion. The preparation was clearly labelled as to its poisonous nature, and workers were instructed to wear protective clothing.

On June 20, 1950, while preparing a lorry tankful of spray solution (24 oz. (680 g.) of the 20% preparation to 500 gallons (2,270 litres) of water), a drop of the 20% preparation splashed on to his forearm, covering an area about the size of a sixpenny piece. He washed it off with water within 30 seconds; this was at 4 p.m. Within a few minutes a raised weal appeared, but no further local injury. During the evening he remained well, took food, and smoked some cigarettes.

At 9.45 p.m. he experienced a sudden severe pain at the back of his head, spreading forward to the forehead. A few minutes later he vomited violently and developed persistent abdominal pain. This was soon followed by a feeling of weakness in the legs, after which he remembered nothing until the next morning in hospital.

He was admitted to Worcester Royal Infirmary at 11.25 p.m. Atropine, 1/60 gr. (1.1 mg.), had already been administered as a first aid, so that the pupils were dilated but reacting. The patient was very drowsy, sweating profusely, and appeared to have violent headache and abdominal pain; his pulse rate was 60 and of good volume; his blood pressure was 110/90; speech was slightly slurred; there was occasional muscular twitching in the upper and lower limbs; respirations were shallow but not distressed.

Dr. V. Keane (then house-physician) continued treatment with atropine sulphate, 1/75 gr. (0.87 mg.) intravenously; then 1/100 gr. (0.65 mg.) hourly for three doses; then two-hourly for two doses; then hypodermically hourly for three doses. In the morning the patient was rational and in the afternoon clinical examination showed him to be normal. He was discharged well on the fifth day after admission.

COMMENT

The patient's history, condition, and recovery on treatment with atropine are indicative of parathion poisoning. His statement indicates that he was aware of only trivial contact with the toxic material, but as parathion is a cumulative poison it seems likely that he had already absorbed and retained a harmful amount before the final intoxication, which was then further aggravated by smoking and by taking food.

The toxic action of parathion and related organic phosphorus insecticides is due to their inhibiting effect on the activity of choline esterase. Atropine is the specific antidote, but the order of dosage required may be much more than the usual therapeutic quantities. In this case a total of 11/100 gr. (7.1 mg.) of atropine sulphate was administered.

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H. B. SALT, M.Sc., A.R.I.C., Biochemist.
Royal Infirmary, Worcester.

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Auricular Fibrillation After Electric Convulsion Therapy

Transient cardiac irregularities are a recognized complication of the various forms of shock therapy employed in the treatment of the psychoses. The following case is of interest because of the prolonged duration of the arrhythmia.

CASE REPORT

A man aged 54 was admitted to hospital in October, 1949, suffering from an agitated depressive state of approximately 12 months' duration. His main complaints were insomnia, inability to concentrate, depression, delusions of guilt and unworthiness, and a feeling which recurred often, and for no reason that he knew, of being urged to strike out at those around him. His blood pressure varied between 230/130 and 150/100, for which fluctuation emotional factors seemed to be largely responsible. No cardiac irregularity or enlargement, tachycardia, or other abnormal physical signs were present clinically.

Electric convulsion therapy was given on alternate days, and was terminated after eight shocks, there being considerable improvement in his mental condition. However, after the last convulsion he complained of palpitation, and on examination

the pulse was irregular, the rate being 110 and the blood pressure 150/90. Electrocardiography confirmed the presence of auricular fibrillation and also showed a minor degree of left axis deviation. This condition persisted for four weeks, with little apparent discomfort to the patient, and then reverted to normal rhythm after quinidine sulphate, 5 gr. (0.32 g.) four-hourly, had been given for four days.

One week later feelings of depression and mental tension had returned. The blood-pressure readings varied between the extremes noted above. Radiological examination of the chest failed to show any definite cardiac enlargement. The electrocardiogram was normal apart from slight left axis deviation. The blood urea was 24 mg. per 100 ml. and the renal clearance (van Slyke) was within normal limits.

In consequence of the mental deterioration, two further convulsions were given at an interval of a week, being preceded on the first occasion by 7½ gr. (0.5 g.) of sodium amytal intravenously, which resulted in a fall of blood pressure from 230/130 to 150/100. For two minutes immediately following the clonic phase in this fit the pulse became irregular, a condition due apparently to premature beats, though electrocardiography was not available to confirm this. The blood pressure, after a transient rise to 180/100, remained within 2 or 3 mm. of 130/85 for 30 minutes afterwards. Oxygen was administered orally throughout.

In the second instance curarization was employed, 22 mg. of D-tubocurarine chloride preceded by 7½ gr. of sodium amytal being given intravenously. A similar fall in blood pressure was noted, but no irregularity. An electrocardiogram taken one minute after the clonic phase showed the left axis deviation and also nodal rhythm for two beats. Other changes were of the type described by Kauntze and Parsons Smith (1948), among others, and consisted of an increase in the height of P_2 and T_2 and depression of the S-T segment in Lead II.

Further convulsive treatment has not been given owing to the improved mental state of the patient.

We wish to thank Dr. E. U. H. Pentreath, medical superintendent of the Pastures Hospital, Derby, for permission to report this case.

P. M. O'FLANAGAN, L.R.C.P.&S.I., D.P.M.
R. B. TAYLOR, M.R.C.S., L.R.C.P., D.P.M.

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Survival of a 16-oz. Baby

Only a few cases are on record of the survival of babies weighing less than 2 lb. (0.9 kg.) at birth. In a survey of the available literature I have been able to trace only six such cases.

De Lee and Greenhill (1943) recorded the delivery of a viable child 182 days after conception, and Ronaldson (1943) one after 189 days. Hoffman, Greenhill, and Lundeen (1938) reported the survival of a baby weighing 26 oz. (0.74 kg.) at birth. Bush (1947) reported the survival of a female infant born at the 27th week and weighing 24 oz. (0.68 kg.) at birth. Browne (1942) quotes the combined weights of the Dionne quintuplets, who were all girls, as 13 lb. 6 oz. (6 kg.), thus giving the average weight of each child as just under 2 lb. 11 oz. (1.2 kg.).

CASE REPORT

A healthy woman aged 31 had her last regular period on June 20, 1948, and there was a slight loss towards the end of July, 1948. She attended the antenatal clinic of the Civil Hospital when four months pregnant. She was well built and nothing abnormal was detected. She was instructed to return to the clinic in a month's time, but failed to do so.

On January 29, 1949, she returned and complained of swelling of the feet and hands which had been present for three weeks. There was no anaemia, albumin was not detected in the urine, and the blood pressure was 130/80 mm. Hg. Palpation of the uterus revealed the presence of three small nodular fibroids, and the fundus was higher than one would expect for the stage of the pregnancy. The woman was admitted to the maternity ward of the Civil Hospital for rest and treatment. She was then 26 weeks pregnant by her date. The day after admission she began to have labour pains, and a female child presenting by the vertex was delivered normally at 7 p.m. on January 30. The third stage was normal and the placenta showed no abnormality. The puerperium was uneventful, and the patient was discharged home on the eleventh day after delivery.

THE CHILD

At birth the infant was very feeble and did not cry. The air passages were cleared with the mucus catheter, and after injecting 1 ml. of nikethamide into the vein of the umbilical cord respirations became well established. The child weighed 1 lb. (0.45 kg.).

As an incubator was not available on the island, the child was wrapped up in cotton-wool and placed in an ordinary cot lined with blankets. The cot was kept warm with hot-water bottles. During the first four days she was fed by pipette with 2 dr. (7 ml.) of glucose water hourly and she took her feeds well. On the third day her weight was still 1 lb. On the fifth to the tenth days she was fed every hour with 2 dr. of expressed breast milk, diluted with its own volume of glucose water. The supply of breast milk then ceased. On the 16th day she weighed 1 lb. 10 oz. (0.74 kg.) and began to give feeble cries.

Since the infant would not tolerate breast milk from other sources, she was given artificial milk. From the 15th to the 38th days the baby was fed two-hourly with 2 dr. of condensed milk diluted with an equal volume of water. She then weighed 2 lb. 12 oz. (1.25 kg.). She was put on dried milk, and has been kept on it since.

The child has progressed satisfactorily, and her weight five and a half months after birth was 6 lb. 12 oz. (3.06 kg.). She was then receiving 4 oz. (114 ml.) of reconstituted dried milk three-hourly, and only six feeds are given in 24 hours.

In addition to her feeds, from birth she was given thyroid. sic., 1/10 gr. (6.5 mg.) daily for 45 days, and dienoestrol, 0.5 mg. daily for 69 days.

The measurements of the infant when only a few days old were:

Distance from crown to heel	13 in. (33 cm.)
Circumference of head	11 in. (27.9 cm.)
Circumference of shoulders	7½ in. (19 cm.)
Distance from umbilicus to pubes ..	¾ in. (1.9 cm.)
Distance from xiphisternum to umbilicus	1¾ in. (4.4 cm.)

X-ray examination of the foot on the 18th day after birth showed the presence of the ossification centres of the calcaneus and astragalus. The centres for the lower epiphysis of the femur and the upper epiphysis of the tibia had not appeared at that time. The femur was *x*-rayed again two months later (on the 81st day after birth) and the centre for the lower epiphysis was present.

I have not found any record of the survival of a child weighing less than 16 oz. at birth.

I wish to thank Dr. A. Rankine, Director of Medical Services, Mauritius, for permission to report this case, and Dr. Y. Cantin, medical superintendent, Civil Hospital, Mauritius, for his advice. Credit is due to Miss G. Davies, matron, Civil Hospital, for her tireless care and supervision and to the nurses of the Civil Hospital for their co-operation in the management of the infant. I would like to thank Mr. L. N. A. Planel, of Glaxo Laboratories Ltd., for supplying the milk powder and the vitamins.

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Reviews

RARITIES

Further Rare Diseases and Debatable Subjects. Edited by F. Parkes Weber. (Pp. 236; illustrated. £1 5s.) London and New York: Staples Press.

This is a companion volume to the one by Dr. Parkes Weber published in 1946, which was welcomed as "a mine of interesting information which may well cause us to think." A further 39 rare diseases or syndromes are described here, and the book closes with a short article on zest in old age.

This is a stimulating volume, valuable to the collector of medical curiosities. Dr. Parkes Weber is well known not only for his abstruse medical knowledge but for his interest in diagnostic problems. The conditions described include such unfamiliar subjects as Sjögren's disease and illuminating accounts are given of more familiar occurrences, such as death while bathing. Those interested in the disturbances of lipoid metabolism will welcome the article on xanthomatosis and arterial atheroma. If "rarity enhances pleasures," many will delight to read this book.

G. E. BEAUMONT.

PSYCHOLOGICAL POLEMICS

Freud or Jung. By Edward Glover. (Pp. 207. 15s.) London: George Allen and Unwin. 1950.

The bewildered doctor who has heard a good deal about Freud and Jung, but has never been able to follow the technical jargon in which their teachings are expressed, may very likely approach this book with the hope that here at last is something which will clear up his ideas and give him new aids in understanding his patients. He will be disappointed, for he will have to be almost as profound a scholar as Dr. Glover himself to understand from this exposition what it is all about. Jung, he will learn, for instance, says that there is only one form of mental energy, which may in its widest sense correspond with *élan vital.* Freud says there are two forms, involved respectively in sexual appetites and instincts towards death and destruction. According to Dr. Glover the first view is false and the second correct, but it would puzzle the reader to understand the argument why.

In his sustained polemic Dr. Glover exposes the nebulosity, vagueness, and self-contradictoriness of the Jungian system, in which psychological, philosophical, and metaphysical elements are all combined. The reader will also be made aware that the Freudian system is much more concrete, closely knit, and logical. It is for that very reason that the Freudian feels that Jung is a threat. Individual Jungian conceptions can be disproved or shown to be meaningless, and other parts of his contribution to psychology may yet stand. If it were once accepted, however, that mental energy is unitary, the whole Freudian house of cards would be in danger of falling to the ground.

One of the faults of Dr. Glover's discussion is that he can find no defect in Freudian doctrine, no good whatever in that of Jung. In his final chapter he issues a serious warning to the eclectic—to the psychiatrist, doctor, or layman who wishes to choose for himself the "best" out of any or all schools. The Freudian system, it is laid down, must be accepted in whole or not at all. This is not the way in which science has progressed, nor is it necessary in the present case. It is perfectly possible to build new theories from fragments taken from Freud and Jung, and any such theory will prove itself less by its internal consistency than by its capacity for making predictions which prove true when subjected to the test of experience. "Who is not with me is against me" is the worst of mottoes for the scientist.

ELIOT SLATER.

TECHNIQUE OF HINGE GRAFTING

The Hinge Graft or Ginglymus Implant. By Arnold K. Henry, M.B.Dubl., M.Ch.(Hon.)Cairo, F.R.C.S.I. (Pp. 64; illustrated. 15s.) Edinburgh: E. and S. Livingstone. 1950.

This small book is about a method of stabilizing certain joints without having resort to arthrodesis. The technique consists essentially in placing a thin narrow strip of cortical bone, with its attached periosteum, longitudinally across each side of the joint to be stabilized. Rigid immobilization is avoided, and progressive movements in the desired plane are encouraged. The bony elements of the grafts break at or near the axis of movement, and a hinged osseofibrous "ligament" is formed along each side of the joint. It is claimed that these ensure lateral stability while permitting free flexion-extension movement. The method has been applied to the treatment of such conditions as instability or deformity of the foot after poliomyelitis, genu recurvatum, and flat-foot. Other possible applications are suggested. No attempt is made to draw definite conclusions from the small number of cases recorded: the author's object has been simply to present the idea and to leave the reader to judge for himself whether or not it is worth pursuing.

Clearly the book's appeal will be mainly to the orthopaedic surgeon. Remembering Professor Henry's masterly work, *Extensile Exposure Applied to Limb Surgery,* most readers will inevitably approach this new book with high expectations. Many will be disappointed. Some, indeed, may wonder whether the hinge graft is really worthy of a book to itself, or whether the author's purpose would not have been served as well by a succinct account of the technique published in an orthopaedic journal. The quality of some of the radiographs falls short of the standard that one has come to expect from this publishing house.

J. C. ADAMS.

FORENSIC MEDICINE

Medical Jurisprudence and Toxicology. By John Glaister, J.P., D.Sc., M.D., F.R.S.Ed. Ninth edition. (Pp. 755; 234 illustrations, 88 in colour. £1 15s.) Edinburgh: E. and S. Livingstone. 1950.

With indefatigable industry the author has kept the ninth edition of this well-known standard textbook thoroughly up to date. It has grown steadily to become a comprehensive source of reference rather than a medical students' handbook, for no student could be asked to measure the subject by this exhaustive standard. The text will nevertheless provide the graduate, specialist, or criminal bar with a sound and authoritative text which incorporates a remarkable amount of detail and reflects current writing over a vast field.

Glaister's painstaking revision includes much new statutory law—the National Health Service and National Insurance (Industrial Injuries) Acts, reviews of Pharmacy and Poisons Law, reference to the liability of hospitals and nursing-homes, to the legality of necropsy, and to artificial insemination. New writing on fingerprints, the coroner, Rh subtypes, blast and blunt head injury, D.D.T., beryllium, and radioactive substances, among innumerable new case

histories and references to current literature, reflects Glaister's determination to keep abreast of forensic advances.

There is a danger that this desire for comprehensiveness will lead to a dichotomy of this valuable textbook—into sections on forensic medicine and toxicology—and this would be a serious disadvantage to the study of what is, after all, one subject. Something must be done to limit its growth: *R. v. Ruxton* could be usefully shortened from its 10 pages; many less pointed illustrative cases might be eliminated and arguments long disposed of be relinquished. The less common subjects such as thallium, copper, borax and cadmium, phosphorus, and fluorine might yield space to the more common. Arsenic can no longer lay claim to 14 pages when carbon monoxide achieves only six (and CO_2, D.N.O.C., or the methyl compounds only a paragraph). This is not a criticism of substance but a plea for a general contraction of what is a most valuable single volume lest it grow unmanageably bulky. "Glaister" remains a fine textbook, maintaining the deep-rooted Scottish traditions in the subject.

KEITH SIMPSON.

PROBLEMS OF PUBLIC HEALTH

Ecology of Health. The New York Academy of Medicine Institute on Public Health, 1947. Edited by E. H. L. Corwin, Ph.D. (Pp. 196. £1.) New York: The Commonwealth Fund. London: Geoffrey Cumberlege.

In 1947 the New York Academy of Medicine held, as part of its Centennial Celebration, an Institute on Public Health, and a number of papers dealing with a large variety of problems were presented. These, together with the discussions of the papers and with some other contributions, have been incorporated in this book to present a survey of modern knowledge and practice in such fields as genetics, maternal nutrition, animal and insect transmission of disease, climate and geography, preventive psychiatry, and public health services. Thus the volume covers a number of fundamental aspects of human oecology, and is concerned with the status of social medicine to-day and with the implications for much-needed research in the future.

The sections into which the material is divided vary considerably both in their comprehensiveness and in their attitudes to public health. In the first section is given a very full and interesting discussion on mutation, and many useful suggestions are made not only on the relation of mutation to mortality but on the effect on morbidity and on the application of genetic theory to public health. The chapter on animal and insect reservoirs of disease will interest workers in the field of public health as much as zoologists and bacteriologists; and the section on maternal nutrition gives a very thorough account of the importance of work being done.

There are necessarily many gaps in this book, not only in respect of the branches of public health which are omitted but in many of the sections given. Much could have been said on the relation of climate and geography to disease, and many useful lines of research could have been indicated. The chapter which discusses the preparation of professional workers is extremely brief, as are also other chapters towards the end of the book.

The accounts given of State and local health services will be of particular interest to many readers in Britain in view of the recent changes in health services in this country. In general, this volume contains such a variety of material and covers so much ground that there will be few readers who will not find in it matters of interest to them.

LILLI STEIN.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Biological Oxidation of Aromatic Rings. Biochemical Society Symposia No. 5. Edited by R. T. Williams. (Pp. 96. 8s.) Cambridge: University Press. 1950.

The British Encyclopaedia of Medical Practice. Edited by Lord Horder, G.C.V.O., M.D., F.R.C.P. Vol. 1. 2nd ed. (Pp. 786. 60s.) London: Butterworth. 1950.

Britannica Book of the Year, 1950. (Pp. 718. 50s.) London: Encyclopaedia Britannica. 1950

The Law and Ethics of Dental Practice. By R. W. Durand, M.R.C.S., L.R.C.P., and D. Morgan, L.D.S. (Pp. 98. 7s. 6d.) London: Hodder and Stoughton. 1950.

The Atlases of Ophthalmoscopy, 1850-1950. By C. W. Rucker, M.D., and T. E. Keys, M.A. (Pp. 31. No price.)

The Scourge of Rheumatism. Report of a conference held by the British Rheumatic Association in September, 1949. Introduction by Lord Horder, G.C.V.O., M.D. (Pp. 85. 5s.) London: William Heinemann. 1950.

Principles of Ophthalmology. By T. Henderson, M.D. (Pp. 230. 20s.) London: William Heinemann. 1950.

Fainting: Physiological and Psychological Considerations. By G. L. Engel, M.D. (Pp. 141. 20s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1950.

Personality in Peptic Ulcer. By A. J. Sullivan, M.D., and T. E. McKell, M.D. (Pp. 100. 21s. 6d.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1950.

The Management of the Patient with Severe Bronchial Asthma. By M. S. Segal, M.D. (Pp. 158. 27s. 6d.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1950.

Races: A Study of the Problems of Race Formation in Man. By C. S. Coon, Ph.D., and others. (Pp. 153. 21s. 6d.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1950.

Fortschritte der Geburtshilfe und Gynäkologie, 1. By W. Neuweiler and others. (Pp. 88. Swiss francs 9.) New York and Basle: S. Karger. 1950.

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ANTIHISTAMINIC DRUGS AND THE COMMON COLD

The common cold has again come unscathed through an ineffective therapeutic attack. The hopes that were initially raised by reports of the value of antihistaminic drugs in the prevention and treatment of colds have received no further support. On the contrary, two reports in this issue of the *Journal* provide convincing evidence that these drugs have little or no effect on the course of a cold. It is not the first time that claims for new cures have proved to be groundless, but in this instance emotions have been aroused unnecessarily and tragedies have occurred which should have been avoided. The first report that antihistaminic drugs appeared to cut short the course of the common cold was that of Brewster[1] in 1947. Since then favourable results have been reported by Brewster in another series,[2] Gordon,[3] Murray,[4] and, notably, Arminio and Sweet.[5] All this work was done in the U.S.A., where, as in England, it was received with a certain amount of scepticism by the profession. Several drug manufacturers, on the other hand, accepted it, and the American public was urged to buy drugs in advertisements which featured such statements as "Sensational new discovery kills colds in hours." The public interest was so great that the Council on Pharmacy and Chemistry of the A.M.A. thought it advisable to review the evidence and issue a report.[6] Two of the papers reviewed were based on clinical impressions without the use of untreated controls, and in Brewster's investigations—which contributed more than half of the total patients studied—the statistics were open to important criticisms. For example, in one much-quoted experiment 20% of the treated cases were given drugs within the first two hours of the onset of symptoms, while only 9% of the controls were observed in this period. The council concluded that further experiment was required, preferably of the sort in which volunteers were inoculated with virus, and that "until a scientifically acceptable study is performed, the true effectiveness of the antihistaminic drugs in the control of the common cold cannot be evaluated." This conclusion created a mild sensation, and the council and the *Journal of the American Medical Association*—which had commented editorially on the council's findings—were berated for expressing their beliefs. It was, in fact, hinted that the medical profession was trying to belittle a cure which patients could buy across the counter without having to consult their physicians.

In the case against the treatment of colds with antihistaminic drugs evidence has since been provided by Cowan and Diehl,[8] who, in a carefully controlled study of students at Minnesota University, obtained the same results in the treatment of colds with a placebo containing citric acid as with phenindamine tartrate, tripelennamine hydrochloride, or ascorbic acid. It is just as well that studies should also have been undertaken in this country, though there has been less public interest in this medical nine-day wonder. To-day we publish the report of a committee of the Medical Research Council on two complementary types of experiment, a small-scale laboratory investigation and a large-scale field trial. In the former, conducted at the Common Cold Research Unit, Salisbury, volunteers were inoculated intranasally with cold virus. Half of the subjects, selected at random, were given chlorocyclizine hydrochloride ("histantin") or promethazine hydrochloride ("phenergan") before and after the inoculations and the other half were given dummy tablets containing a small dose of phenobarbitone. Neither the patients nor the clinical observer knew what any particular patient had received. The results were clear cut; full doses of powerful antihistaminic drugs neither prevented colds nor had an effect on the nature of the cold when once it was established. However, the number of volunteers who took part in this trial was small, and the result of the field trial was, in its way, more impressive. For although the diagnoses could not be determined with absolute confidence, and were in fact with certain limitations dependent on the subjective feelings of the patients, there was the compensatory advantage that the drug was given an opportunity of showing whether it had any effect on any group of what may have been a heterogeneous mixture of diseases. The drug used in this experiment was thonzylamine, and it was given in the same dosage as was reported on so favourably by Arminio and Sweet. Medical officers at nineteen centres took part in the investigation, and 1,550 volunteers with colds were treated. They reported to the medical officer concerned or to his assistant as soon as possible after the first symptoms began, when they were given an envelope containing three tablets with instructions how to take them. They saw the doctor again on the two following days, when they were given further supplies

[1] *Nav. med. Bull. Wash.*, 1947, **47**, 810.
[2] *Illinois med. J.*, 1949, **96**, 302.
[3] *Laryngoscope, St. Louis*, 1948, **58**, 1265.
[4] Murray, H. G., *Industr. Med.*, 1949, **18**, 215.
[5] Ibid., 1949, **18**, 509.
[6] *J. Amer. med. Ass.*, 1950, **142**, 566.
[7] Ibid., 1950, **142**, 570.
[8] Ibid., 1950, **143**, 421.

of tablets, and finally one week after their first visit. Half the patients received antihistaminic drugs and half received dummy tablets containing a trace of quinine, but neither the patients nor the medical workers knew what sort of tablets any particular patient received.

To ensure that neither patients nor doctors can identify drugs in trials of this kind it has usually been considered sufficient to give the two sets of tablets a code sign and to choose alternate patients for each type of treatment. This method, however, has the disadvantage that if one of the types of tablets comes to be recognized the investigation ceases to be blind and the possibility of bias arises. In the M.R.C. trial, the reported side-effects of the antihistaminic drugs might conceivably have given a clue to the nature of the tablets, and another method was therefore adopted. The tablets were made up centrally into sets and each set was numbered at random. Since the key was kept centrally until the investigation was finished it was impossible for anyone to know what any individual had received while his progress was being assessed, and even if a correct guess could be made in one instance no light was thrown on any of the others. The results showed that thonzylamine "had little if any value in the treatment of the common cold." The only element of doubt was introduced by the observation of just significant differences (in the technical sense) between the treated and control groups at the end of the first day's treatment, a difference which, however, had disappeared by the end of the second day. This may be interpreted as indicating that a small number of patients with allergic rhinitis (rather than with true colds) were inadvertently included in the series and that these patients had responded to treatment. In any case the difference is so slight that, even if real, it is of little practical importance.

Also published in this issue is a paper by Drs. G. Lorriman and W. J. Martin describing another carefully planned and well-controlled clinical experiment. The drug used was "antistin," and the results were essentially the same as those obtained by the M.R.C. committee: the only difference was that no trace of an effect was obtained on any day of treatment. It is remarkable that side-effects were as common with the placebo as with the drug, despite the full doses given—a feature which was also noted by the M.R.C. workers. Cowan and Diehl's comment on human suggestibility is apposite:

"We have received many enthusiastic reports . . . from the subjects of the cold study. However, some of the most glowing testimonials came from members of the control group. The first request we received this fall concerning information on the availability of our cold pills came from a student who had been in the study series. . . . He made a special trip from the northern part of the State to get the drug, whereupon it became necessary for us to look up his record. He had been in the placebo group."

In this country we have been fortunate that there has been a spirit of co-operation which has prevented over-enthusiasm on the part of the manufacturers—and here it should be emphasized that there are no doubts whatsoever about the value of the antihistaminic drugs in their right place. There have, however, been individual tragedies. The pressure of public opinion, which is sensitive to news from afar, resulted in the open sale of antihistaminic drugs and their storage in many domestic cupboards. In some instances children have found the tablets, sampled them, and died. Such events are always tragic, but are the more so when the drug would not have been of any use for the condition for which it was bought.

EMOTIONS AND THE COLON

It is common knowledge that disorders in alimentary function which often resemble those resulting from organic disease can be caused by emotional stress. Recent work sheds light on the mechanisms concerned. In experiments on 39 healthy volunteers Almy and his colleagues[1] investigated the functional state of the sigmoid colon by proctoscopic examination or by pressure-recording with inlying balloons. The stimuli applied were cold pain, produced by immersion of the hand for five minutes in ice-cold water; head compression with a headscrew; insulin-induced hypoglycaemia; or discussion of real or imagined disturbing events in the subject's life. In about half of the subjects such stimuli caused stronger contractions of the colon, with hyperaemia and increased mucus secretion. In all who reacted thus there were associated emotional reactions and bodily changes such as sweating, pallor, and a rise in blood pressure. Of those whose sigmoid colon remained functionally unchanged, only two showed general signs of stress, and usually there was close correspondence between the degree of colonic change and the intensity of the general reaction. With all four experimental stimuli the colonic response appeared to be related, not simply to the stimulus itself, but to the subject's attitude towards it—the response occurring only when the subject believed his personal security to be threatened.

In a further investigation[2] the same technique was used in studying patients with spastic constipation which became worse during periods of emotional strain. Comparable results were obtained, but the authors found that the colon responded most vigorously when the patients were upset by discussion of emotional problems and difficult life situations. Strong wave-like colonic contractions were often recorded, but these were

[1] *Gastroenterology*, 1949, **12**, 425.
[2] Ibid., 1949, **12**, 437.
[3] *Amer. J. digest. Dis.*, 1941, **8**, 197.
[4] *Gastroenterology*, 1949, **13**, 547.
[5] *Amer. J. med. Sci.*, 1949, **217**, 241.
[6] *J. Amer. med. Ass.*, 1950, **142**, 1044.

non-propulsive because they occurred simultaneously in more than one place, an observation in accord with the finding of Adler and his colleagues[3] that the majority of colonic waves are non-propulsive for this reason. Thus the response of the colon to emotional strain in both normal individuals and those with spastic constipation is the same, though symptoms occur only in the latter, probably because of the greater intensity and duration of their reactions. Occasionally the source of strain may lie in some disturbing emotional situation, but more commonly tension arises because of the patient's neurotic traits which make him see danger where none exists. Sufferers from colonic spasm are generally sensitive and immature, adapting with difficulty to environmental stress, exacerbations of symptoms often being related to feelings of anxiety, resentment, or guilt. Thus the seat of the trouble lies not in the bowel but in the patient's conflict with his environment. His is a normal bowel reaction to abnormal stress. In a detailed study of the personalities of twenty patients with ulcerative colitis Mahoney and his colleagues[4] found that they presented an abundance of neurotic traits. Such terms as "autonomic imbalance" and "neuromuscular dysfunction" are therefore misleading, and treatment should be along psychiatric lines.

Lysozyme, a mucolytic and bacteriolytic enzyme, is normally present in human tears, nasal mucus, and gastro-intestinal secretions. When fed to dogs it causes acute ulceration of the upper intestinal tract. Grace and his colleagues[5] have recently shown that anxiety, apprehension, anger, hostility, and resentment are associated with variations in faecal lysozyme, particularly when these emotions are repressed. Moderate transient increase occurred in normal individuals in such moods. In sufferers from ulcerative colitis, however, marked and sustained rise in lysozyme production followed emotional upheaval, and the symptoms became worse as the faecal-lysozyme concentration increased. When the disease was in remission lysozyme concentration was low. Normal amounts of the enzyme were found in patients with carcinoma of the colon and mucous colitis. In a patient with a permanent colostomy small circumscribed areas of oedema and inflammation were observed after human tears containing lysozyme had been applied with cotton-wool pledgets for 24 hours. The authors therefore suggest that because of its mucolytic action excessive lysozyme may play an important part in causing colonic ulceration, and, further, that lysozyme production fluctuates with the emotional state of the individual. Grace, Wolf, and Wolff[6] have confirmed and amplified these findings in a particularly well-planned study of four subjects with colostomy. They found that unexpressed anger and resentment were associated with colonic hyperfunction, which was shown by hyperaemia, engorgement, hypermotility, and increased secretion of both mucus and lysozyme. In this state, which resembled that caused by the administration of methacholine chloride, the fragility of the colonic mucosa was much greater than normal. Sustained feelings of anger and resentment leading to continued colonic hyperfunction resulted in submucosal petechial haemorrhage and ulceration. This demonstration of the resemblance between gastric and colonic function under emotional stress helps to a better understanding of the importance of the psyche in the genesis and aggravation of ulcerative colitis, and it confirms Maudsley's dictum that "the sorrow which has no vent in tears may make other organs weep."

HEALED BACTERIAL ENDOCARDITIS

It is now five years since penicillin has been available in this country for the treatment of subacute bacterial endocarditis, and it is therefore possible to consider what the outlook for successfully treated patients is likely to be. In a paper published elsewhere in this issue Dr. H. Matthew makes such an assessment on the basis of cases treated in Edinburgh. It has hitherto been believed that, despite eradication of the infection, a patient's expectation of life may be short owing to the severe damage caused to the affected valves: as a result of inevitable fibrosis and contracture a valve may conceivably be more incompetent when the disease is over than it was when the infective process was active. The two cases of aortic valve disease described by Rosenblatt and Loewe[1] in a paper quoted by Matthew were striking examples of this change: cusps were reduced to mere stumps, the valve being consequently almost functionless. For this reason the final prognosis has been regarded as most favourable in patients with endocarditis not involving a valve, particularly in those whose underlying abnormality is a patent interventricular septum.

Matthew's follow-up study of the Edinburgh series will serve as a corrective to any undue pessimism in this matter. There were 20 patients out of a total of 40 treated who survived for periods varying from 2¼ to 5¼ years. Only one of these patients has died, the cause of death being heart failure and the lesion aortic stenosis. Of the remainder, none has relapsed or become reinfected. A study of their exercise tolerance shows impairment in only two, and an increase in the size of the heart has been observed in only four: all but two are engaged in the same occupation as before their illness or another no less strenuous. Two, whose lesion was pulmonary stenosis, have actually benefited, their capacity for exercise being greater than before the onset of the disease. It appears that the practical effect of the infection has been to reduce the degree of stenosis. In short, the majority of these patients are as well as they were before their disease developed. If an opportunity eventually occurs of examining their heart valves doubtless the sort of fibrosis and calcification will

[1] *Arch. intern. Med.*, 1945, **76**, 1.

be present which is occasionally seen in patients who are not known to have had bacterial endocarditis—a finding which is the chief support of a belief that spontaneous cure of this disease can sometimes occur.

These are very encouraging findings, but it is important to understand that they are based on a study of patients who had already survived for 2¼ years. The fate of 20 other patients in the Edinburgh series who did not survive for this length of time is not discussed in this paper. In fact congestive heart failure, due mainly to gross valvular damage, is most liable to develop actually during the course of treatment or, as Matthew says, "shortly afterwards." It is of some interest to know how long a period is covered by this term. Contracture following reparative changes should be well advanced within two to three months, and it would therefore be expected that heart failure consequent on it should show itself within that time if a gross degree of valvular incompetence were the result. In Rosenblatt and Loewe's two patients, already referred to, death occurred five and six months after treatment had begun. Evidently some such period as this should elapse before it can safely be concluded that the final prognosis is favourable.

CONGENITAL MALARIA

Malaria in the foetus infected by its mother before or during parturition has long been recognized. Plasmodia have often been detected in the peripheral blood of infants at birth, or at any time up to the shortest recorded "incubation" period for the species of parasite concerned. In other cases parasites have been demonstrated in the brain, liver, spleen, or heart's blood of the foetus. As long ago as 1866[1] deposits of malarial pigment were found in an infant at a necropsy performed three hours after birth. More than 100 papers have been published on this subject, but the only extensive series of observations are on the native populations of hyperendemic areas, where the predominant malarial parasite is *P. falciparum*, and where, though there is a high incidence of heavy placental infections, congenital malaria is for the most part extremely rare. Thus Clark[2] in Panama recorded one case in 400 births, Blacklock and Gordon[3] in Sierra Leone none in 173, Garnham[4] in Kenya none in 404, Walton[5] in Sierra Leone 7 in 2,154, and Peel and Van Hoof[6] none in 403.

These findings have created an impression that congenital malaria is everywhere a very rare event, but records for foreign (non-immune) residents in malarious areas show that in them the disease may be less uncommon than has generally been supposed. Dr. B. S. Jones puts forward evidence to support this view in a paper published elsewhere in this issue: three cases of congenital malaria were found among 37 infants born to European women in February, 1949, at a hospital in Lagos. Most of the published reports are of isolated cases, and there are no data available from which the incidence of malaria among non-immune individuals can be accurately calculated. The three cases recorded from Lagos were all due to infection with *P. falciparum*, but a number of infections with *P. vivax* and a few with *P. malariae* have been described.

The mechanism of transmission of congenital malaria is still not fully understood, but it has been generally assumed that the parasites pass from the maternal to the foetal circulation as the result either of mechanical damage to the placenta or of pathological changes in it induced by malarial infection. The reason why congenital malaria is so very rare among natives of hyperendemic areas though relatively common in non-immune subjects has been the subject of much speculation. Schwetz[7] suggested that the greater frequency in non-immune individuals is due to the greater friability and permeability of the placenta caused by febrile malaria. In the cases recorded by Jones, however, only one of the three mothers admitted to any recent malarial attack. Peel and Van Hoof suggested that the enormous numbers of phagocytes observed in the placentae of natives might be an obstacle to the transplacental passage of the parasite. This is in harmony with the view put forward by Jones that with increasing immunity the efficiency of the placenta as a barrier to foetal transmission increases, and the incidence of congenital malaria therefore falls.

EARLY DIAGNOSIS OF DISSEMINATED SCLEROSIS

The diagnosis of disseminated sclerosis is relatively easy when multiple lesions are found in the central nervous system and when the history indicates that they appeared at varying intervals of time. But in the early stages, and particularly when only one symptom is complained of, the diagnosis may be very difficult, and at times can be only presumptive. The diagnosis remains essentially a clinical one, based on the findings at examination and, more particularly, on the study of the way in which the disorder has progressed. A carefully compiled case history is essential. No pathological or radiological test is of value except in so far as these may help in excluding other types of neurological disease. In a few cases the finding of a completely normal cerebrospinal fluid except for a first-zone or "paretic" Lange gold curve may provide some confirmation of the clinical diagnosis if the Wassermann reactions in the blood and C.S.F. are negative. In a paper published elsewhere in this issue Drs. D. K. Adams and J. M. Sutherland and Mr. W. B. Fletcher have analysed the presenting symptoms in 389 cases of disseminated sclerosis, and they agree with previous authors that the most common early symptoms are weakness of one or more limbs, visual disturbances, paraesthesiae, vertigo, and disorders of micturition. The incidence of retrobulbar neuritis as an initial symptom was 13.9%, which is lower than the 20% recorded by Müller[1] in his remarkable recent study of 810 patients in Sweden. They suggest that the disease occurs most frequently in sympatheticotonic individuals and

[1] Thomas, L., *Arch. Heilk.*, 1866, **7**, 307.
[2] *J. exp. Med.*, 1915, **22**, 427.
[3] *Ann. trop. Med. Parasit.*, 1925, **19**, 327.
[4] *Trans. R. Soc. trop. Med. Hyg.*, 1938, **32**, 13.
[5] *Ann. trop. Med. Parasit.*, 1947, **41**, 434.
[6] *Ann. Soc. belge Méd. trop.*, 1948, **28**, 413.
[7] *Bull. Soc. Path. exot.*, 1939, **32**, 44.

[1] *Acta med. scand., Suppl.* 222, 1949, **133**.
[2] *Brit. J. Ophthal.*, 1944, **28**, 40.

that vasomotor disturbances, such as coldness of the hands and feet, and chilblains, are common in the early stages. Frequent early signs which they found in the eyes were imbalance of the ocular muscles, enlarged pupils, and hippus. The first of these, as demonstrated by the two eyes moving at different rates when the patient looks to one side, is a valuable sign of disturbed function of the posterior longitudinal bundle, and when ataxic nystagmus is also present the sign is almost diagnostic of disseminated sclerosis, as Harris[2] has noted. Mydriasis and hippus are quite commonly found in apparently normal people, while the latter is often noted in patients with Sydenham's chorea: it would therefore seem to be unwise to give prominence to these findings in the diagnosis of disseminated sclerosis. Temporal pallor of the optic disks was recorded in only 16.5% of the 79 cases investigated in hospital—a figure corresponding fairly well with the incidence of retrobulbar neuritis in the whole series—and many neurologists will agree that too much is made of this physical sign in some textbooks, especially since it is difficult to assess slight degrees of temporal pallor. Adams and his colleagues rightly emphasize the importance of impairment or absence of the superficial abdominal reflexes when the abdominal musculature is good, even when the plantar responses are flexor. In disseminated sclerosis these reflexes disappear in the early stages of a pyramidal lesion, while in some other neurological disorders, in particular amyotrophic lateral sclerosis, the abdominal reflexes may remain unaffected even when there is spasticity of the legs with ankle clonus and extensor plantar responses.

It is obviously desirable to diagnose disseminated sclerosis in the earliest stage of the disease, when the lesions are potentially reversible. But at the present time, when there is no specific treatment and indeed no therapy which can for certain modify the pathological process or the natural history of the disease in any way, there is a definite danger in attaching the diagnostic label of disseminated sclerosis to a patient on inadequate clinical grounds. Too frequently, when this diagnosis has been made, little further thought is given to the possibility of the diagnosis being wrong, and patients with more readily treated conditions, such as subacute combined degeneration of the cord, myasthenia gravis, and spinal cord tumours, are left untreated.

DOCTORS' HANDBOOK

The new edition of the B.M.A. *Medical Practitioners' Handbook*[1] is an invaluable compendium for the medical practitioner, whatever branch of medicine he practises. Though it is described as not a complete work of reference, it will answer most questions about medical practice, and indicate the sources to consult for the rest. The last edition was published 15 years ago, and many new special sections have been added to cover the changes that have taken place in recent years. The simple, though still fundamental, guidance given in the Hippocratic Oath appears in its opening pages, and the great complexity of medical practice to-day is reflected in the subsequent advice given on such topics as ethical conduct, the administration of the Health Service, business agreements between practitioners, and the legal obligations of doctors to the State. Since hardly any of this information is taught to medical students, newly qualified doctors will find the *Handbook* an indispensable companion to their medical textbooks—and incidentally be thankful that they were not examined on its contents in their Finals, so intricate has the legal and administrative side of medical practice become. The more experienced doctor will find many useful addresses, and the solutions to problems that perhaps crop up only once in a lifetime, while for the postgraduate student details are given of special courses and diplomas. The *Handbook* is well bound and printed, and will stand up to the hard use it is sure to receive.

[1] *The Medical Practitioners' Handbook* British Medical Association, 1950.

ON COUGHING UP CALCIUM

Erosion of calcified glands into the bronchi is known to be one of the rarer causes of haemoptysis, but it is surprising to read that Schmidt[1] and his colleagues consider that broncholithiasis has been of great interest to the medical profession for centuries. To justify this statement they have collected from the Mayo Clinic 41 cases in which calcified material was either coughed up or discovered during endoscopic or surgical procedures. Most of the patients were over the age of 40, and the presenting symptoms were usually cough and haemoptysis. Haemoptysis, the first symptom in nine patients, was severe enough in six to require treatment by blood transfusion. Other distressing symptoms were severe retrosternal pain, thought to be caused by bronchial colic, and intractable asthma. The most characteristic radiological finding was a focus of calcification in association with an area of segmental pulmonary collapse, penetrating radiographs often being necessary to demonstrate the calcium. In other cases there were merely single or scattered areas of calcification.

The term broncholithiasis is perhaps unfortunate, since stones are not formed within the lumen of the bronchus. Bronchial stones are always produced by the ulceration of peribronchial calcified material through the bronchial walls. Schmidt and his colleagues confirm the popular belief that much the commonest source of such material is calcified tuberculous lymph nodes; they give, as rarer causes, coccidioidomycosis and histoplasmosis, neither of which is of great importance in this country. The authors also suggest that the calcified bronchial cartilages so often seen in old age may sometimes separate off into the bronchi, but they do not make it clear that such a process was found in any of their cases.

The importance of stones in the respiratory passages is that the resulting symptoms and signs are apt to be confused with those of other pulmonary disorders, especially bronchial carcinoma. Indeed, the differentiation may at times be exceedingly difficult, since radiography is not conclusive, and bronchoscopy often reveals fleshy granulomatous tissue round the calcified mass. Thoracotomy and exploration may be necessary when doubt exists, though needless operation might be prevented by careful questioning. Almost half of Schmidt's patients gave a history of coughing up stones; one patient claimed to have performed this unusual feat no fewer than 103 times.

[1] *J. thorac. Surg.*, 1950, **19**, 226.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

CHEMOTHERAPY—I. ADMINISTRATION OF PENICILLIN

BY

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In describing the therapeutic use of penicillin it is convenient to deal first with its administration and secondly with indications for it : these will be the subject of a succeeding article.

Therapeutic Action

Two theoretical aspects must be considered briefly : one of these is the nature of the action of penicillin. This is exerted exclusively on the bacteria causing the infection, and varies in nature and degree with the concentration to which they are exposed. Low concentrations do little more than inhibit bacterial growth, but one only 5 or 10 times greater than this is actively, though not very rapidly, bactericidal : 99% or more of a fully exposed bacterial population may be killed within a few hours. If the concentration is increased beyond this point no further acceleration of bacterial death occurs, and with certain organisms the rate may even be substantially decreased. Penicillin is unique in this behaviour. It has an optimum concentration for antibacterial effect beyond which an increase will certainly be useless and may be positively detrimental, whereas with other bactericidal substances increased concentration accelerates effect indefinitely. The optimum concentration for a sensitive organism is quite low—for a staphylococcus about 0.1 unit per ml., and for a haemolytic streptococcus even less. It might appear from this that the object of treatment should be to maintain this concentration in the tissues until the infection is eliminated. In the first place this is impossible except by the use of a continuous drip. It further overlooks the fact that penicillin has to diffuse into infected areas, where the concentration is likely to be lower than that attained in the blood. The view is widely held that the intermittent production of relatively very high blood levels is useful in promoting this diffusion into undrained abscesses, areas of necrosis, cardiac vegetations, etc.

How long should this action be maintained, and should it be continuous or intermittent ? There are grounds for believing that the necessary duration of treatment depends on two principal factors. One is the sensitivity of the organism : the gonococcus, the most sensitive of all, can usually be eliminated in a few hours. The other is the total number of bacteria to be disposed of, which is tantamount to saying the stage or extent of the infection. At a very early stage the dose required may be only a small fraction of that necessary later. The relative merits of continuous and intermittent effect have been much debated and are still unsettled. Penicillin acts only on multiplying bacteria, and since any given dose leaves a number of semi-dormant bacterial cells alive (Bigger's "persisters") it is argued that these should be allowed to begin multiplying before another is given. It would obviously be dangerous to carry this policy too far. It is known that bacteria exposed to but not killed by penicillin resume growth in a period averaging three to four hours, and it seems reasonable not to allow the concentration in the blood between doses to fall below an effective level for much longer than this. Recent extensive therapeutic tests in animals support this view.

Absorption and Excretion

The ordinary salts of penicillin (the sodium salt being that commonly used) are freely soluble and highly diffusible. Injected in watery solution into the tissues, penicillin is quickly absorbed, reaching maximum concentration in the blood within less than 15 minutes if the dose is not very large. This rise to a high level is followed by a fall at first almost as steep, due to rapid renal elimination. Penicillin leaves the body as fast as it reaches the kidneys, and the enormous quantities which have to be given are due to the fact that on the average each molecule spends only a few minutes in the circulation between absorption from the injection site and excretion by the kidney. Comparatively few ever reach and still fewer remain at the site of a local infection. That the doses given are enormous will be conceded when it is remembered that in a patient of average weight with total anuria the dose required to produce an adequate concentration in the blood for treating a fully sensitive infection would be only 350 units. It is advisable to bear in mind that patients with impaired renal function require smaller doses at longer intervals.

The rate of fall in the blood level, although steep at first, progressively diminishes. During the latter part of this phase traces are probably still being absorbed from the site of injection, and some which has passed into the tissues is returning to the circulation via the lymph. The relation of duration of effect to dose, and means of obtaining more prolonged effect, are discussed later.

Treatment by Intramuscular Injection

Penicillin may be given either by continuous infusion—now an uncommon practice, and feasible only in a hospital—or by spaced single injections. It is usual to make these intramuscularly, but this route was originally adopted because the crude penicillin of early days was more painful given subcutaneously. This objection to the subcutaneous route no longer holds, and it has some slight advantage in being followed by rather slower absorption. The site of injection is theoretically indifferent, and practically so in a well-nourished patient requiring few injections. In an emaciated patient having a long course, rotation of the main sites is essential. In either, skill and a really sharp needle affect his reaction considerably.

It was originally the practice to give small doses at intervals of three or at the most four hours in order to maintain the effect. With the free availability of penicillin the practice has grown up of giving large doses at long intervals, and this has been carried to greater lengths in this country than in any other. It is important to know how far this is justified, and in considering this it must be remembered that duration of effect is by no means directly proportional to the dose given. The larger this is, the greater the rate of elimination, and doubling the dose actually prolongs effect by only about one-third. The following are the approximate times during which a detectable and thus—for a sensitive infection—therapeutically useful concentration persists in the blood.

After	25,000 units	.. ..	2½ hours
,,	50,000 ,,	.. ..	3 ,,
,,	100,000 ,,	.. ..	4 ,,
,,	250,000 ,,	.. ..	5 ,,
,,	500,000 ,,	.. ..	7½ ,,

These figures are only approximate, because the rate of elimination varies inexplicably in different apparently normal subjects. They conflict in the higher range with other published figures, but the last of them is based on recent observations by a colleague and myself made by an accurate technique in a series of 31 individuals, and we have no hesitation in asserting that for a dose of 500,000 units to produce a detectable blood level after the eighth hour is exceptional.

It has already been mentioned that bacteria are known to take some hours to recover from exposure to penicillin and to resume growth, the length of this period varying with species, length of exposure, and concentration. Allowing for this factor, the following intervals are appropriate between different doses for patients in whom it is necessary that the drug should exert a full and uninterrupted effect.

Dose		Interval
25,000 units	.. ..	3 hours
50,000 ,,	.. ..	4 ,,
100,000 ,,	.. ..	6 ,,
250,000 ,,	.. ..	8 ,,
500,000 ,,	.. ..	12 ,,

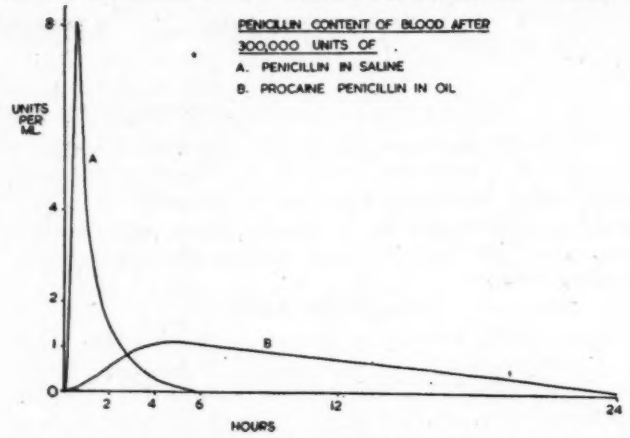
In less serious cases, and when frequent administration is impracticable, these intervals may be lengthened, probably with some retardation of the therapeutic effect, but it seems inadvisable in any circumstances to give penicillin in this form only once daily : the interval for bacterial recovery is then too long. It is true that penicillin persists in exudates after it has disappeared from the blood, and this may add a few hours to the period of efficacy of each dose, but it is not known how far this persistence depends on the nature of the lesion and the rate of exudation into it, and there are some conditions, notably bacterial endocarditis, in which this factor is not operative at all.

Slowly Absorbed Preparations

The effect of a single dose can be prolonged either by delaying absorption or by blocking excretion. Various substances have been used which interfere with the renal excretion of penicillin. Of these the most useful is caronamide, since it can be given by the mouth. The dose required is large, and apt to cause nausea and other disturbances. This method should be used only under hospital conditions for sustaining very high blood levels in unusually resistant infections.

Delayed absorption was first secured by suspending calcium penicillin in an oil base also containing beeswax. Beeswax is essential for the full delaying effect, and it is this ingredient which causes local reactions, sometimes going on to suppuration. These preparations are now almost entirely superseded by oily suspensions (containing no beeswax) or powders, suspended in water before injection, containing procaine penicillin. This compound of the two substances has a low solubility to which its slow absorption is mainly due, and an antibacterial action equivalent to that of penicillin itself. The rate of absorption—and, it may be added, the facility with which the material will pass through a small needle—depend on the size and shape of the procaine penicillin crystals : it is possible, although not all manufacturers have yet succeeded in doing this, to produce crystals large enough (50 μ in diameter) to dissolve slowly, but so compact as not to cause needle blockage.

The rate of absorption of a good preparation of this kind is contrasted with that of an ordinary solution of sodium penicillin in the accompanying figure. After a



dose of 250,000 units or thereabouts the blood level rises to a maximum of about 1 unit per ml. in four hours, then diminishing very slowly so that an effective or at least detectable amount is still present after 24 hours. If the preparation also contains aluminium stearate, a water-repellent substance which delays absorption further, this shallow curve is even more flattened, and penicillin may be detected in the blood after two days or even considerably longer if a large dose (one million units or more) is given. Some of these preparations also contain sodium penicillin, which will also give a high initial level lasting only a short time.

The object of these preparations is to secure a continuous effect from a single daily dose, from doses given at intervals of two or more days, or even to cure an infection by a single dose which need not be repeated. They provide much the simplest means of treating patients efficiently in their own homes, where only infrequent injections are feasible. They may be used in a patient under nursing care either because a continuous fairly low blood level is thought desirable, or simply in order to obviate frequent injections. What they will not do is to produce a high blood level. If the infection is a relatively resistant one, or if for any other reason it is thought desirable to achieve a blood level of much over 1 unit per ml., then large doses of sodium penicillin should be given.

Oral Administration

Penicillin is destroyed by acid in the stomach and by bacterial enzymic action in the lower bowel. There is also some loss, not wholly explained, in the upper part of the intestine, since, even in patients with total achlorhydria or given penicillin through a duodenal tube, only a fraction of the dose is absorbed. It is therefore necessary to give from 5 to 10 times the intramuscular dose in order to achieve the same effect; even so the effect is not altogether dependable, since the proportion absorbed varies inexplicably in different subjects, and even in the same subject at different times. Absorption is better when the stomach is empty : oral penicillin should therefore be given before meals. Antacids and various capsules designed to overcome the acid gastric barrier have not been found helpful. Absorption is rather more constant in infants, and penicillin may be added to feeds. Here there is the double advantage of avoiding injections in patients to whom they are most disturbing, and of reasonable economy, since the dose required is comparatively small on a body-weight basis.

It is difficult to say what place this form of treatment should have, but even its more enthusiastic advocates are reluctant to employ it in serious cases owing to the uncertainty of its effects.

Local Administration

There are many ways in which penicillin may usefully be applied to the actual site of infection. Besides being a chemotherapeutic agent, it has all the properties of the ideal antiseptic, killing or preventing the growth of susceptible bacteria without doing the slightest harm to tissue. Local application may be indicated for its simplicity and economy, because the area concerned can be reached in no other way, or in order to attain a high concentration there which will persist for some time. The following are the more important examples.

Intrathecal Injection.—Only traces of penicillin reach the cerebrospinal fluid from the blood unless enormous doses are given intramuscularly. Meningitis should therefore be treated by intrathecal injection as well as intramuscular. Pure ("white") sodium penicillin should be used, and the solution should be prepared freshly with the strictest aseptic precautions and with no preservative such as phenol. A dose of 10,000 units will maintain an adequate level for 24 hours. Unless there is a block, remarkably uniform diffusion occurs throughout the central nervous system from an injection given by the lumbar route.

Serous Sacs, Joints, and Abscesses.—Penicillin solution may with advantage be injected into an empyema cavity, a joint affected by suppurative arthritis, or abscess cavities elsewhere, the dose depending on the size of the cavity: as much as 100,000 units may be indicated for a large empyema. Absorption from such an area is slow, and penetration into it from the blood equally or more so; this is therefore not only a convenient but the only way of keeping up a high concentration in such a collection of fluid for a whole day or more. If the dose is large, slow absorption will also maintain a systemic effect, to some extent taking the place of intramuscular injections. This is not the place (nor am I the person) to discuss the surgical treatment of these conditions further than to say that penicillin does not necessarily remove the need for it.

Carbuncle can be treated very successfully by injecting penicillin into and around it. Even though the solution also contains procaine, this is a painful proceeding, but may be well worth while to accelerate resolution.

Wounds.—One way of preventing infection in a recent wound is to dust it with a powder containing penicillin. The usual diluent is a sulphonamide (preferably sulphathiazole), and the procedure has been objected to on account of the risk of causing sensitization. Established sepsis in superficial wounds and burns, if due to a demonstrably sensitive organism, may be treated similarly, or by the spraying of a solution or the application of a cream. These last two methods are applicable, under the same condition, to the treatment of infections of the skin. Among other superficial infections, conjunctivitis may be treated by drops frequently applied or by lamellae.

Upper Air Passages.—Infections of the main nasal cavity (it being remembered that the sinuses are generally inaccessible to such measures) can be treated either with a spray or, probably better, by the frequent use of a snuff containing 5,000 units of calcium penicillin per gramme of sulphathiazole. This has been particularly successful in clearing up nasal carrier conditions; and, owing to the backward flow of mucus in the nose, it has also an effect on the nasopharynx and even the throat.

Local treatment of the throat and mouth is best carried out with gelatin pastilles, one of which should be kept in the buccal sulcus throughout the day. Solution is slow, and replacement necessary at intervals of not less than an hour. The official trochiscus penicillinae of the *B.P.*, a tablet with a lactose base, is less satisfactory. The choice of this product was dictated by the greater stability of penicillin in a dry form, but gelatin pastilles are now obtainable which retain the greater part of their activity for months; alternatively, they can easily be made fresh by a pharmacist. Penicillin chewing-gums are also suitable for this type of use if the patient will persist with them.

Infections of the bronchi and lungs may be treated by inhalation, a small volume of concentrated solution containing, say, 100,000 units being administered by a Collison or other inhaler several times a day. There is some absorption by this route: thus a large enough dose will also exert a systemic effect. The inhalation of a fine powder of penicillin, recently advocated in the U.S.A., has not apparently been adopted in this country, and seems likely to be more disagreeable to the patient than a liquid spray.

PHARMACY AND POISONS ACT, 1933

The Poisons List Order, 1950 (S.I. 1950, No. 1213) and the Poisons Rules, 1950 (S.I. 1950, No. 1214), which were made by the Secretary of State on July 21, come into operation on September 1. These Statutory Instruments make the following changes in the Poisons List and the Poisons Rules, 1949, hereafter called the Principal Rules.

Part I of the Poisons List and the First Schedule to the Principal Rules.—The following substances are added: Alphaprodine; its salts. The following antihistamine substances and their salts: antazoline, diphenhydramine, 3-di-*n*-butylaminomethyl-4:5:6-trihydroxyphthalide, phenindamine, substances being tetra-substituted N derivatives of ethylenediamine or propylenediamine. Betaprodine; its salts. Di-isopropyl fluorophosphonate. Hydroxypethidine; its salts. Isoamidone; its salts. Ketobemidone; its salts. Methadol; its salts. Methadyl acetate; its salts. Polymethylenebistrimethylammonium salts. The following items are amended: Amidone (DL-2-dimethylamino-4:4-diphenylheptane-5-one); its salts. The chemical description is omitted and the entry now reads: "Amidone; its salts." The item "6-morpholino-4:4-diphenylheptane-3-one; its salts," which describes the poison now known as phenadoxone is omitted, and after the item "Pethidine; its salts;" there is inserted "Phenadoxone; its salts."

The Third Schedule to the Principal Rules.—Antihistamine substances and their salts are added to Group II of this Schedule and are thereby exempted from the requirements of the Pharmacy and Poisons Act and the Principal Rules when in the form of "preparations intended for external application only."

The Fourth Schedule to the Principal Rules.—Antihistamine substances and their salts, other than the preparations exempted by inclusion in Group II of the Third Schedule, and polymethylenebistrimethylammonium salts are added to this Schedule. The item "6-morpholino-4:4-diphenylheptane-3-one; its salts" is deleted from this Schedule. This poison (under the name phenadoxone) is now subject to control under the Dangerous Drugs law.

The Seventh Schedule to the Principal Rules.—At the end of this Schedule the following paragraph is added: To be labelled with the words "Caution. This preparation should be administered only under medical supervision. The vapour is dangerous": Medicines made up ready for the internal or external treatment of human ailments and containing di-isopropyl fluorophosphonate.

Rules 7 and 12 of the Principal Rules.—These Rules are amended to provide that when a poison is supplied in ampoules the "signed order" or prescription may state either the total amount to be supplied (as at present) or the total amount intended for administration or injection.

Rule 16 and the Thirteenth Schedule to the Principal Rules.—In paragraph (*e*) of the proviso to this Rule and in the Schedule the description "executive officer" is replaced by the description "county agricultural officer or assistant county agricultural officer."

Copies of the Poisons List Order and of the Poisons Rules may be obtained from H.M. Stationery Office or through any bookseller.

INFANT-FEEDING IN NORTH-EAST AFRICA*

BY

LESLIE HOUSDEN, O.B.E., M.D.

Nearly all infants are breast-fed, especially in the southern half of the Sudan. In the northern half western influence and customs have already begun to give native mothers western views. A woman will occasionally come to hospital with her baby already off the breast, saying that her milk was no good. In Somaliland the fathers sometimes demand that their babies shall be given undiluted cows' milk, believing that it makes them "more lively." These fathers also have a way of sending their wives into the interior to look after the stock, leaving the young infants to the care of the grandmothers.

Deprived of breast milk in the early months of life—as through the death of the mother—infants rarely survive. Alternative food is difficult to find, especially in the milkless tsetse-fly country, and is usually unsuitable both in quantity and kind. Overfeeding and malnutrition go hand in hand. Sometimes the young infant is fed on porridge made from sweet potatoes or groundnuts, with additions of mango juice during the mango season, which may last from April until July. In countries where cows' or camels' milk is obtainable, it is usually very dirty, and gastro-enteritis is a common cause of death. Tea, ghee (clarified butter), rice, and chewed fat are other forms of infant food.

[Photograph by Dr. John Bloss

FIG. 1.—Mother comforting her child.

*Notes based on experience in the Anglo-Egyptian Sudan and British Somaliland.

[Author's photograph

FIG. 2.—Baby shielded by half-gourd on mother's back.

Breast-fed Too Long

The chief fault of native nursing is that it is continued too long. Two years is a very usual time, and often the child is breast-fed up to the age of 3 or 4. Early progress is usually good, especially if the mother is herself reasonably well nourished, but after the age of 8 or 9 months the baby ceases to do well and later still loses ground. Often the mother is undernourished and ill, especially in Somaliland, where the standard of nutrition is low and infants of 18 months have been found in an emaciated condition, starving on 6 or 8 oz. of breast milk a day.

There are several reasons for this prolonged nursing. First there is the difficulty of alternative feeding in lands where milk is scarce or unknown and where adult food is unsuitable for infants and often insufficient for the adults themselves. Then there is the physical contact with their mothers in which infants spend so much of the first two years of their lives. They live attached to their mothers. They use neither cot nor cradle. By day they are carried slung to the mother's back or side, at night they lie against her as she sleeps. Whenever a baby cries he is fed. One of the objections to the use of a cradle is that the mother thinks her baby should not leave her. A third reason is that in some tribes husbands do not engage in sexual intercourse with a wife who is nursing a baby. Prolonged breast-feeding therefore acts as a method of birth control.

It is not the prolonged breast-feeding that harms the native infant but breast starvation. After a grossly inadequate intake of breast milk over many months the infant is marasmic and anaemic and ready to succumb to the diarrhoea set up by unsuitable foods at weaning. If additional foods were given the breast milk would be a boon. In some tribes additional foods are given. Zande mothers, for instance, sometimes give scraped banana, with or without water, from the seventh day. They also chew sugar-cane and spit it into the baby's mouth. From one month, dura (millet) porridge and chewed sweet potato and cassava may be given. Other Zande mothers, however, give nothing until they add porridge at the ninth month. During these nine months the mothers themselves take nothing but gruel and simsin (a vegetable oil). Among the Shilluks a mother may not drink milk for the first six months of pregnancy lest the cow from which the milk came goes dry.

Hazardous Gardening

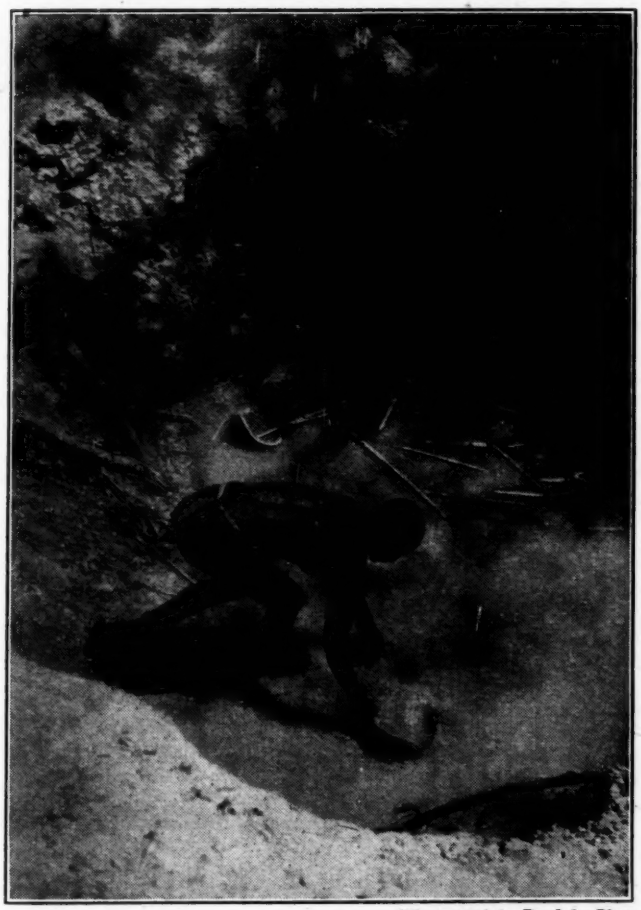
Complementary foods, such as oranges and lemons, sweet potato, banana, millet, and local fruits such as pawpaw, are either obtainable or could be produced if fathers had the will and energy to grow them, but even when they are available the mothers are often unwilling to give them. They say that their babies will not eat them, and continue

to underfeed them on the breast. In some parts there is a further difficulty in persuading the fathers to provide the needed foods, the popular belief being that if anyone produces a garden better than all the others he will die the same year.

Native babies spend the greater part of their first two years in close contact with their mothers' bodies. When the baby cries or when the mother has nothing else to do, her infant is fed. There are no regular feed-times; the breast is available at all times of the day and night. This close maternal contact is maintained as long as the mother has the baby's welfare uppermost in her mind. During the rains, when she may join the rest of the tribe in cultivating the land, she will leave her baby all day with no food at all, to be carried about on the back of an elder brother or sister, crying for food until she returns. The elder brother or sister provides the physical contact usually supplied by the mother but cannot produce the food.

The only other time when the breast is unavailable to the baby is when the mother is drunk. This is a common occurrence in some areas.

The age of weaning varies according to the tribe, the time of year (i.e., the state of cultivation), and chance, but the most usual food at all times is porridge made from



[Photograph by Dr. John Bloss

FIG. 3.—Woman drawing water by means of half-gourd from water-hole.

dura (millet). This requires hours of grinding by hand between two stones if a fine flour is to be produced, but mothers are often unwilling to spend so long over its preparation. They use it for their infants in an incomplete and gritty form. It causes diarrhoea, which is lethal to marasmic and anaemic infants.

Infant Death Rate

In North-east Africa there are few vital statistics—and they are unreliable. There are, however, well-founded impressions. One of these is that in some parts the death rate of infants during the first two years of life is between 50% and 60%. Some natives forget very quickly that they had any children who died, but some figures of value can be produced. In February, 1949, fourteen chiefs of the Torit area had had 186 children, of whom 87 were still living. This was an infant- or child-mortality rate of 53.2%. One Somali interpreter had had by his eight wives 42 children, of whom 18, that is 43%, had died "from some kind of sickness." The eight wives of another interpreter had presented him with 35 children, of whom 22 had died, a mortality rate of 63%. A Somali medical assistant had lost seven out of nine children with "diarrhoea and abdominal pain." Very little is thought of these high death rates. As a Sudanese medical assistant said, "When ill-nourished, anaemic babies get any intercurrent disease, they die. No one ever thinks of natural death."

Infant Welfare

In many parts of the world where black-skinned people dwell there are too many people; in some there are too few. Torit in Equatoria (Anglo-Egyptian Sudan) is one of these, and on May 7 the Save the Children Fund sent a team of one doctor and two nurses to spend the next few years in teaching the local tribes how to keep their babies alive. Although in principle the saving of these infants will be simple, in practice there will be difficulties.

The logic of infant welfare will appeal only to those who have logical minds. It is good to make certain simple preparations for the reception of a baby, but many native mothers believe that if any preparations at all are made for an unborn baby it will surely die. A father should grow food for his children, but, besides his likely death the same year if his garden excels those of his neighbours, he must guard his crops day and night as they reach maturity or they will be stolen. Western ideas of dealing with native problems must be modified by the native outlook. The study and research of the Save the Children Fund team should produce information of interest and value.

A circular from the Ministry of Health states that hospital boards sometimes acquire property with moneys from their endowment fund with the intention of selling or renting the property to the Minister when it is required for hospital purposes, but the Minister warns boards that he cannot acquire a property for which a price has been paid in excess of that appropriate to a compulsory purchase. Nor can he purchase any property for which such an excess price has been paid, even though the board offers to resell to him at the compulsory-purchase price, the loss being taken by the endowment fund, and he cannot rent, lease, or accept a gift of such a property. The Minister is bound to carry out the intentions of Parliament as expressed in Part V of the Town and Country Planning Act, 1947, and he could not take part in a transaction which would undermine the provisions of that Act. This should be remembered whenever a board is buying from the endowment fund property which might be suitable for hospital purposes; and if the board is likely one day to wish to sell, lease, rent, or give such property to the Minister it should consider whether it is advisable to pay a price in excess of the district valuer's valuation of the property. Boards do not at present know what the district valuer's price would be, as his services are available only where purchase by a Government Department is in view. The Minister has therefore arranged that any board may ask him to request the chief valuer to make the services of the district valuer available to the board.

Reports of Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS

Scientific Meeting at Leeds

The 44th Scientific Meeting was held at Leeds on July 20, 21, and 22 under the presidency of Dr. NORAH SCHUSTER. The inaugural session was devoted to a consideration of allergic diseases of blood vessels. Dr. G. DISCOMBE (London) reviewed 16 proved and 6 suspected cases of polyarteritis nodosa. Laboratory investigations did not always help in the diagnosis, for biopsy was sometimes negative. Lesions might heal, and, if in the kidney, could produce an essential hypertension the changes of which might almost completely obliterate those of polyarteritis nodosa. Eosinophilia, although common and usually demonstrable by direct counts during the active phase, was not an essential part of the syndrome. Dr. W. PAGEL (London) discussed some unusual aspects of histology and the question of aetiology. Subendothelial swelling due to permeation of fluid seemed to be followed by exudation of fibrinogen with subsequent necrosis, mostly eccentric, of the vessel wall, a breach in which became plugged with fibrin. Fibrin was deposited, too, both inside and outside the necrotic wall. He preferred to reserve the term "fibrinoid" for changes which failed to show the staining affinities of fibrin, and which sometimes occurred in positions which did not always favour the assumption that one was dealing with fibrin which had lost its staining affinities. In his opinion the differences between polyarteritis nodosa and the "pararheumatic" diseases, including lupus erythematosus disseminatus, dermatomyositis, and temporal arteritis, were more in the natural history of the disease and the preferential site and distribution of the basic change rather than in the basic histology, which appeared to be identical. In polyarteritis nodosa extramural foci involved the collagen fibres and were indistinguishable from the acute infiltrative changes in rheumatic fever, lupus erythematosus disseminatus, and dermatomyositis. In some instances healed polyarteritis nodosa appeared to be the basis of an eosinophil-celled alveolitis (Loeffler's syndrome) associated with exfoliative dermatitis and asthma (in one case terminated by cerebral haemorrhage). Intradermal injection of heat-killed streptococci in healthy persons and in rheumatic and other patients who had volunteered had established the significance of bacterial antigens in the reproduction of the changes characteristic of polyarteritis nodosa. Both the histological and experimental evidence supported the view that polyarteritis nodosa and the related diseases were an expression of the hyperergic response to any aetiological factor, including bacterial (notably streptococcal) antigen.

Dr. I. RANNIE (Newcastle-upon-Tyne) described the value of biopsy. A positive result was obtained in 8 out of 12 cases, the four unsuccessful biopsies being explained by either the unsuitability or the insufficiency of the material submitted. In 5 of the 8 positive instances biopsy was carried out for confirmation of diagnosis; 4 were taken from the muscle, and 1 from a skin nodule. The diagnosis of polyarteritis nodosa was established as a chance biopsy finding in the remaining 3 cases, the organs submitted being respectively appendix, liver, and cervix uteri and ovaries. Muscle was the material of choice; a tender area should be chosen for excision, and a negative report should not be issued until serial sections had been studied.

Professor T. CRAWFORD (London), discussing the experimental production of polyarteritis nodosa, said that there were two main types of procedure which had led to the production of lesions in animals closely resembling those of polyarteritis in man. The first, introduced by German pathologists about 1930 and used extensively by Rich and Gregory in the U.S.A., consisted in the administration of foreign protein to a suitable animal such as the rabbit. The second, described in this country by Wilson and Byron, depended upon the production of hypertension by some procedure such as the clipping of a renal artery in rats. The interpretation of these experiments which the speaker favoured was that the first procedure led to a tissue antigen-antibody reaction characterized by necrosis and fibrin deposition in the vessel walls and a cellular reaction around the injured area; whereas with the second procedure sudden elevation of blood pressure caused damage to the less well supported arteries, and this again led to necrosis and fibrin deposition in the vessel wall, with a secondary cellular response as in the former lesion. When considered in conjunction with knowledge gained from clinical sources, the first of these experimental procedures seemed to constitute a closer parallel to the conditions of the human disease than did the latter. Study of these lesions might well lead to better understanding of the human disease and of the effects of various agents upon it.

The sessions which followed provided a varied programme. Short papers were read by Dr. G. B. S. ROBERTS (Glasgow), Dr. I. FRIEDMANN (London), Dr. T. B. MAGATH (Rochester, Minnesota), Drs. R. AIDIN and G. H. TOVEY (Bristol), Dr. R. W. FAIRBROTHER (Manchester), and Air Vice-marshal T. C. St.C. MORTON (Wendover).

Dr. SCHUSTER, whose presidential address was entitled "Nec silet mors," told of the increasing demands which advances in medicine and surgery made on pathologists who undertook necropsies; to-day they must needs pay attention to parts of anatomy which 25 years ago they could safely ignore. As a profession doctors were always willing to learn, but it was comforting to know that at the age of 80 Leonardo da Vinci was to be seen passing through the streets of Milan on his way to the medical school to refresh his memory on points of anatomy. A full medical and occupational history was essential for the pathologist at the time of the necropsy, otherwise there might be great wastage of material.

Non-pulmonary Tuberculosis

Dr. G. S. WILSON (London) gave an account of the survey that was carried out in England and Wales during 1943–5 into the distribution and frequency of non-pulmonary tuberculosis caused by the bovine type of bacillus. The survey was an excellent example of what could be achieved by co-operation between different laboratories making use of ordinary routine material, and Dr. Wilson took the opportunity of thanking the 149 pathologists who had gone to the trouble of collecting specimens for examination by the bacteriologists. In England strains from 994 patients had been examined; of these, 26.3% belonged to the bovine type. The percentage distribution according to site of disease was: meninges 27.1; cervical glands 46.5; bones and joints 10.8; genito-urinary system 12.8; miscellaneous 10.6. The proportion of bovine-type strains was highest in the second quinquennium of life, and higher among females than males. It was calculated that in England and Wales during 1944 about 24% of all cases of non-pulmonary tuberculosis were of bovine origin and that 1,300 to 1,400 persons died of milk-borne tuberculosis. In conclusion Dr. Wilson drew attention to the high proportion of mistaken diagnoses in cervical adenitis, and suggested that further work was required to distinguish the tuberculous from other forms of the disease. Dr. G. STEWART SMITH (Exeter) spoke on the problem of non-pulmonary tuberculosis as seen in an urban and rural community in the south-west.

Dr. A. J. RHODES (Toronto) gave an account of the epidemiology of the Coxsackie virus and of a recent epidemic in Dufferin county in which both the viruses of poliomyelitis and of the Coxsackie infection appeared to take part. Dr. F. O. MACCALLUM (Colindale) described briefly the results of recent investigations made on material sent in to the Virus Reference Laboratory, and the problems of diagnosis which faced us to-day. Other papers on a variety of subjects were read by Dr. J. B. FOOTE (London), Dr. P. G. WALKER and Mr. R. D. WILKINS (London), Professor C. H. GRAY (London), Drs. E. M. DARMADY, J. HARKNESS, and A. RICHARDSON JONES (Portsmouth), Dr. C. J. YOUNG (Bradford), Dr. OSCAR B. HUNTER, jun. (Washington, D.C.), Dr. C. MERSKEY (Oxford), and Dr. J. V. DACIE (London). Speakers at the dinner of the association, which was held on July 21, included Professor MATTHEW STEWART and Dr. ROBERT A. MOORE, professor of pathology at the Washington University, St. Louis, Missouri, and secretary of the American Board of Pathology.

Correspondence

Haemorrhage from Peptic Ulcer

SIR,—Your readers must be tired of the bandying about of statistics on the results of the treatment of haemorrhage from peptic ulcer, but I should like to raise the question whether these haemorrhages need really occur. If every peptic ulcer, once definitely established as chronic, was operated upon "in the cold" there would be few or no bleedings or perforations, the total mortality from the disease would probably be less, and patients would be saved those years of semi-invalidism which the so-called medical treatment of peptic ulcer involves. Such at least is my belief.—I am, etc.,

Streatley, Berks. ROBERT HUTCHISON.

SIR,—In neither of the two articles on haematemesis in the *Journal* (July 15, p. 138) is any mention made of aspirin as a cause of acute peptic ulcer and haemorrhage. There is no doubt that aspirin tablets swallowed whole can have this effect and that cases are now occurring. Arthur Hurst may have over-estimated its frequency, but since his death this factor seems to have been forgotten. Unless the possibility of aspirin tablets having been taken in this manner is specially inquired for, it is most unlikely that it will be mentioned by the patient. It should be borne in mind by those studying the aetiology of peptic ulcer and compiling statistics on haematemesis.—I am, etc.,

London, W.1. HENRY TIDY.

Reflections on Criminal Conduct

SIR,—Sir David K. Henderson's paper "Reflections on Criminal Conduct and Its Treatment" (August 5, p. 311) is a miracle of clarity and good sense such as one might have expected from its source. I am sure that sooner or later his conclusions will become universally adopted. For example, his view that a man medically insane should be regarded as legally insane is a case in point. One certifies a man because he is dangerous to himself or others, yet if he kills someone when confined in a mental hospital he is liable for trial! Was there ever such an illogical position? To my mind a person suspected of insanity who is accused of a crime should be examined before the trial and certified if he is insane. The certificate should be checked by the Board of Control, and if necessary by further independent specialists. If the prisoner is insane he should be regarded as unfit to plead, and sent to a mental hospital. This would prevent the recurring argument over the M'Naghten rules, which, as Sir David points out, are anomalous and antiquated. Juries in my experience are absolutely unable to give a reliable opinion on a prisoner's sanity. I have given evidence in the case of a man whose mental age was eight years, who had confirmed epilepsy, and who did a senseless crime in either an epileptic rage or in a state of automatism. The jury found him guilty. I wrote to the Home Secretary and pointed out that under the Lunacy Acts he must have the prisoner re-examined on the information submitted. He did so, and the man was found impossible to hang humanely because he had a wooden leg! Recently in the face of three doctors' evidence, which included the prison doctor, that he was schizophrenic, a man called Rivett was twice found guilty of murder, his appeal was disallowed, and Lord Justice Goddard praised the jury system—presumably for disregarding medical evidence.

The treatment of sexual offences in court is most extraordinary. I have seen men discharged with a caution by a magistrate for exactly the same offence as received a heavy sentence from a judge. Psychotherapy, which is often very successful in these cases, is allowed grudgingly, if at all. Yet I have treated five cases of exhibitionism during the past two years and not one offended during that time; and everyone who treats sexual cases knows that many respond well to proper therapy.

It is to be hoped that Sir David's valuable paper will be perused by the legal profession, particularly magistrates and judges who have the ultimate disposal of prisoners, so that they have some idea at least of the trend of medical thought since the formulation of the M'Naghten rules 107 years ago.—I am, etc.,

London, W.1. CLIFFORD ALLEN.

SIR,—I yield to no one in my admiration for Sir David K. Henderson's article, but venture on the strength of almost fifty years in practice—for twenty of which I held a prison appointment—to make the following remarks. The clash between lawyer and doctor in these cases is due to each looking at it from his own narrow or specialized viewpoint. All agree that society must be protected: the lawyer says "by incarceration in prison and/or death"; the psychiatrist says "by incarceration in hospital and/or castration"; but these measures are only justifiable, surely, if decreed by a society that is itself blameless. My experience in the years I served in prison as a medical officer was that the more intelligent the prisoner the more emphatic he was that his only extra sin was that of being found out. He confessed readily to hard luck and even to stupidity in allowing himself to be caught, but he remained convinced that in a competitive society where one man's weakness was the other man's opportunity—jungle law, in fact—he was no worse than the judge, jury, lawyer, and doctor who had sent him to jail. In all honesty, Mr. Editor, was he far wrong?

I regret that I cannot agree that the psychiatrist and/or his unit, which Sir David advocates, would yield any result sufficient to justify its inevitable expense. I may have been unfortunate in my experience, but I have seldom or never known of any case being cured by these agencies. I find that attendants and attended, if long enough together, gradually approximate to each other mentally till in time they find a common level. How can it be otherwise?—I am, etc.,

Glasgow, E.1. JAMES COOK.

SIR,—The masterly memorandum by Sir David K. Henderson and your leading article on the causes of delinquency are of great general interest. But to study the problem should we really insist, as might be thought from your article, on classification by types of reaction rather than by types of person? If we consider the equation which expresses type of reaction as the product of environmental stress on a particular type of person, surely it is equally necessary to make adequate records of the other two variables—namely, the person and his burdens.

I would have welcomed some reference in your article to William H. Sheldon's recent book[1] giving detailed biographies of 200 delinquent youths side by side with their somatotype photographs. Sheldon claims that the confusion in psychiatric nomenclature can be reduced by reference to morphology, and the subject made thereby intelligible. His system of somatotyping is governed by objective standards. Types of reaction are found to be closely linked in precise and numerical terms with type of physique. Moreover, he points out that where psychiatrists have repeatedly disagreed about the diagnosis of a particular case the patient's physique lies half-way between the two body types associated with the conflicting diagnoses of types of reaction. These claims are big, but well enough substantiated in his book to warrant at least investigation by other workers.

Stott argues that we ought to begin with the study of the normal before we turn to the delinquent, and it is this which leads me, as general physician in charge of an undergraduate health service, to take the cue. After somatotyping more than 300 undergraduates and completing a short scale-index of temperament, together with a record of the signs of neurosis, it is clear to me that the main substance of Sheldon's work showing the closeness of association between physical type and temperament and the prevalence of signs of neurosis is sound. I should recommend that the use of somatotyping or similar photogrammetric methods be included in any comprehensive scheme for future research into the causes of delinquency. It might, for example, help in time to resolve the perennial argument about the efficacy or suitability of corporal punishment,

and do this by distinguishing those for whom it is unsuited from those whose physique and temperament will stand up to corporal punishment or will even benefit from it. Although somatotyping will provide information about only one aspect of this very complex problem, yet I must emphasize that in studying the delinquent, just as in studying the normal, a positive and objective record of what the subject is himself is likely to be as essential as recording the stress of his environment or the type of his reaction.—I am, etc.,

Oxford. R. W. PARNELL.

REFERENCE

1 *Varieties of Delinquent Youth*, 1949, Harper, New York.

Typing of Bact. coli

SIR,—Your annotation (July 22, p. 205) draws attention to the present confusion in nomenclature of the two serological types of *Bact. coli* found during recent years in association with infantile diarrhoea and vomiting. These types are commonly known as *Bact. coli* alpha (or as *Bact. coli neapolitanum, Bact. coli* D 433, etc.) and *Bact. coli* beta. Your annotator suggests that Kauffmann's notation could be adopted with advantage, and, on the basis of the identification of the somatic (O) antigen, gives the two types the more definitive names of *Bact. coli* O group 111 and *Bact. coli* O group 55 respectively. He does not discuss, however, the criteria upon which these designations should depend. Clarity on this point would seem essential if accurate and comparable results are to be obtained.

To some bacteriologists absorption tests would appear necessary, at this stage of our knowledge, for the confirmation of the O group. These procedures, however, are not practicable in the identification of the large numbers of strains sometimes obtained in clinical and epidemiological studies. Direct tube agglutination titrations present certain difficulties with regard to absolute and relative end-points (see Wramby, 1948), and may involve a consideration of partial antigenic components and overlapping reactions. Further, it may be recalled, certain "paracolon-like non-lactose-fermenters" have been agglutinated to titre by a *Bact. coli neapolitanum* serum (Bray, 1945). In any case, tube titration tests, in addition to biochemical tests, would prove too time-consuming for many laboratories.

Slide agglutination with impure K sera (prepared with living organisms and therefore of a complex nature) is the method usually employed to-day for the detection of *Bact. coli* alpha and beta colonies on primary culture plates. One fears that, unless the distinction is understood, "detection" may come to be regarded as the equivalent of "identification." The further risk then exists that strains detected by slide agglutination may be assigned, without further investigation, to a *Bact. coli* O group. Drs. A. M. M. Payne and G. T. Cook (July 22, p. 192) record that the first isolations of *Bact. coli* D 433 from 15 infants in a residential home were subjected to biochemical test and were agglutinated to titre by *Bact. coli* D 433 K and O sera; in subsequent isolations from the same infants, however, "the identification of *Bact. coli* D 433 was made by slide agglutination only." In all, 25 (or 62%) of the 40 strains recorded by them as *Bact. coli* D 433 would appear to have been subjected to this test alone. The nature of the serum used for the slide agglutination test is not stated, but it was presumably a K serum. It is not clear how many of these strains have been classed in your annotation as *Bact. coli* O group 111.

The same authors state that a study of the literature reveals that strains of *Bact. coli* α-type isolated by several groups of workers during recent years are, in fact, antigenically identical, and that they are the same as that described in their own paper. Establishment of antigenic identity among these organisms requires consideration of the O, B (see Smith, 1949), and H (see below) antigens, and, so far as I am aware, complete antigenic determinations have not as yet been made in this country. In order that present and future workers may follow clearly the developments of work in this field, I would suggest that, when "serological identity" is reported, accompanying reference should be made to the nature of the antigens determined and the methods used for their determination.

At the present time I am making an investigation of the H antigen(s) of a number of *Bact. coli* alpha strains isolated in the course of a clinical and bacteriological study undertaken in collaboration with Dr. A. T. Roden. Thirty-one of the 144 infants admitted to one gastro-enteritis ward in 1949 yielded *Bact. coli* alpha strains from rectal swabs taken in the admission room. The 31 infants were all suffering from diarrhoea and vomiting. The 31 strains all produced, within 24 hours, acid and gas in glucose, lactose, maltose, and mannite, and, within a few days, acid and gas, or acid only, in sucrose, salicin, and dulcite; all were indol +, M.R. +, V.P. −, citrate −, and urease −; and all were agglutinated to titre by *Bact. coli* alpha O and K sera. All 31 strains were motile, most of them highly so, when subcultured in Craigie tubes of soft nutrient digest agar. An H serum, prepared with a formolized suspension of one highly motile strain, gave "large-flake" agglutination and had a titre of 1/12,800 with the homologous strain and with certain of the other strains but not with all of them. It has not been possible to draw conclusions from these results, since as yet the observations are few and the techniques far from refined.

Four other infants, in the same series and also suffering from diarrhoea and vomiting, yielded atypical *Bact. coli* alpha strains from rectal swabs taken in the admission room. These four strains failed to conform to the characteristic biochemical pattern of the typical strains in two, three, four, and five particulars respectively. They were all agglutinated to titre by *Bact. coli* alpha O and K sera. Three of them were actively motile in peptone water, but did not show significant agglutination with the *Bact. coli* alpha H serum. In contrast to the typical *Bact. coli* alpha strains which were "O-inagglutinable" (i.e., not agglutinated in the living state by homologous O serum), the four atypical strains were, in varying degree "O-agglutinable" (i.e., agglutinated in the living state by homologous O serum). Attempts are being made to produce a *Bact. coli* B serum by the employment of one of these "O-agglutinable" strains for absorption.

Among the *Bact. coli* beta strains isolated during the course of the investigation the three following patterns of fermentative activity have been observed: (*a*) rapid acid and gas in sucrose; slow acid and gas, or acid only, in maltose; (*b*) rapid acid and gas in maltose; slow acid and gas, or acid only, in sucrose; (*c*) acid only in seven commonly used "sugars."

The variants and sub-types of *Bact. coli* alpha and beta would seem to merit further attention, since it is possible that in time they might be found to have some clinical or epidemiological significance. The number of atypical strains may prove to be not inconsiderable. Based on comparatively few tests, 11% of the *Bact. coli* alpha strains, isolated from infants on admission to one gastro-enteritis ward during one year, were found to show variation from the type strains and from one another.

There are two lines of approach to the existing and coming problems in the investigation of *Bact. coli* types associated with infantile diarrhoea and vomiting. The first is the advancement of knowledge by fundamental research regarding their antigenic components, their biochemical reactions and other properties, their variants, and their sub-types. The second is the development of simplified techniques designed to meet the needs of the many bacteriologists who are showing an interest in the work and who are anxious to bring the typing of *Bact. coli* strains within the scope of their laboratories. It is particularly in connexion with antibiotics trials and cross-infection studies that this need is being felt. Between the simple but insufficient slide agglutination test and the time-consuming full agglutination and biochemical tests it may be possible to devise a standardized typing technique applicable to everyday use. An inclusion of the determination of the somatic antigen would be of value, because then the O group, as your annotator suggests, could be made the main antigenic component, to which other factors could be added as knowledge grows.—I am, etc.,

Tottenham, N.15. JOYCE WRIGHT.

REFERENCES

1 Bray, J., *J. Path. Bact.*, 1945, **57**, 239.
2 Kauffmann, F., *J. Immunol.*, 1947, **57**, 71.
3 Smith, J., *J. Hyg., Camb.*, 1949, **47**, 221.
4 Wramby, G., *Acta path. microbiol. scand.*, 1948, Suppl. lxxvi.

Value of Tuberculin-jelly Tests

SIR,—Dr. W. Pointon Dick's article on this subject (*Journal*, July 15, p. 141) has escaped my previous notice owing to absence on holiday. I would like to take this opportunity of confirming his findings, first as to the value of an abrasive technique before applying the jelly, and secondly of the superiority of an old tuberculin (O.T.) jelly over one whose active constituent is purified protein derivative (P.P.D.).

Since I originally published the method of skin abrasion (sand-papering) in 1946, I have carried out many series of jelly tests on known Mantoux-positive reactors, and have found fairly consistently that the technique of skin abrasion increases the number of positive reactions about 20% over the technique in which abrasion is not used, and yields results comparable to the 1:1,000 Mantoux using O.T.

As regards Dr. Dick's second point, I too have found that a jelly made up of O.T. gives superior results to one containing P.P.D., even using the latter in double strength (i.e., 4 mg./g.), and would recommend that all tuberculin jellies used for skin testing should have old tuberculin as their active constituent.—I am, etc.,

Appley Bridge, near Wigan. E. H. W. DEANE.

Infection by Syringe

SIR,—Some fourteen years ago I was initiated by Dr. Bousfield into the technique of diphtheria immunization and Schick-testing, and since then have been regularly employed in immunizing and testing children from 9 months to 15 years. His letter (August 5, p. 365) was therefore of special interest, for, quite independently, I have during the last few weeks been employing just the technique he suggests—i.e., taking up into the syringe a small overdose and pumping out the excess before refilling the syringe. There is, however, yet another safeguard which for years past has invariably been employed in this area—namely, rapidly passing the needle two or three times through the flame of a spirit-lamp before taking up fresh antigen. We have had no mishaps so far over the years, and the mild local reactions that occasionally follow injection are promptly controlled with a cold saline compress.—I am, etc.,

Haywards Heath. H. L. DUKE.

Obstetrical Anaesthesia

SIR,—While welcoming Dr. J. G. Warnock's support (July 22, p. 218) for my contention (July 1, p. 47) that in domiciliary midwifery the left lateral position is far safer than the lithotomy position for forceps delivery, I would at the same time very readily respond to his invitation to suggest a simple technique which could, I think with advantage, replace chloroform in midwifery, though the method I practise is not original, and may be even disappointing in its simplicity.

First, however, perhaps I may be allowed a few words of comment on his letter. His successful record, on which he is to be congratulated, of freedom from the calamity of primary cardiac failure in his whole series does not mean of course that light chloroform anaesthesia is free from that risk in operative procedures, even in obstetrics. I well remember seeing a sudden death from primary cardiac failure while chloroform was being administered by an expert during a simple stretching of the sphincter ani.

It is not so long ago since a case was recorded in this *Journal* of a woman of 25 whose heart stopped just as the child had been delivered by forceps under chloroform anaesthesia. In this instance the doctor performed cardiac massage by Nicolson's method in circumstances which allowed only the use of an unsterilized scalpel and unwashed hands, and the patient recovered. The case was recorded, very naturally, as a triumph for cardiac massage, though it might well have been published as a warning in respect of the chloroform which unquestionably was the cause of the disaster.

The technique which I use is simply the substitution of ether for chloroform, either by the open method or in a Clover's apparatus, and I have had no mishaps during the whole of thirty years of general practice involving a good deal of midwifery. I do not believe that an open fire in the room need deter one from using ether, but, of course, its potentialities must always be borne in mind and certain common-sense precautions must be observed. These include: (1) adequate ventilation; (2) the site of anaesthesia must be remote from the fire, and this may involve moving the bed; (3) the fire should be rendered "dead"—actual flames are the real danger; (4) in rare instances it may be necessary to have the fire removed in a bucket—if, for example, the room is very small; (5) a gas fire should be turned out during the anaesthetic. I make no apology for detailing these precautions, as they are of crucial importance.

In low-forceps delivery the degree of anaesthesia can be diminished once forceps have been applied, for light ether anaesthesia has no inherent dangers, whereas deep ether anaesthesia, if prolonged, and still more deep and prolonged chloroform anaesthesia carry the risk of post-partum inertia and haemorrhage.

In support of ether I should like to quote Dr. John Elam, whose contribution to anaesthesia as a general-practitioner anaesthetist is unique. He writes:

"Ether is unquestionably the safest and best anaesthetic for the general practitioner to administer for a forceps delivery, the repair of the perineum, or the removal of an adherent placenta. Ether can be safely left in the hands of a midwife once the induction has been accomplished."[1]

With this I am in entire agreement, though I would add to his last paragraph the words "provided the patient is lying in the left lateral position."

The objection that is sometimes raised that ether is unpleasant to take is met by the fact that all anaesthetics are well tolerated during labour, and in actual practice one finds that when, during delay in the second stage, the indications for forceps are fulfilled the patient cares little what anaesthetic is used so long as it is efficient in relieving the pain.—I am, etc.,

London, N.W.7. A. H. MORLEY.

REFERENCE

1 *Post.-Grad. med. J.*, 1946, **22**, 269.

Mongolism in One of Twins

SIR,—The following report may be of interest in adding another case of mongolism in one of twins to the scanty literature on this subject.

I attended the mother on May 19, 1938, when she had her first pregnancy. A healthy male child was born, and this child has developed normally. On March 17, 1943, I was in attendance for her second confinement, when she was delivered of twins. She was then 38½ years of age. There have been no miscarriages. The pregnancy was uniovular, with separate amniotic sacs, and the sex was female in each. There was no obstetric difficulty and the delivery was at full time. The mongolism in the one twin is of a very severe degree, and although now 7 years old her weight is only 19 lb. (8.6 kg.). She is unable to walk, stand, or crawl, and sits all day in a leaning-forward position. She is still bottle-fed, and as yet there is no evidence of any permanent teeth. The circulation in the hands and feet is very poor, but there is no congenital heart defect. The other twin has developed normally and is of a good average intelligence, likes arithmetic, reading, and music, but does not show outstanding ability in any particular subject.

—I am, etc.,

Middleton-in-Teesdale, Co. Durham. ROBERT DAWSON.

Crisis in Tuberculosis

SIR,—We treat live patients, not dead ones. To calculate bed requirements on the basis of mortality rates (see *Journal*, July 29, p. 295) is to presume a constant ratio between those developing tuberculosis and those dying from it. In fact, the evidence suggests that this ratio grows steadily larger; on the one hand more cases are diagnosed, and on the other a smaller proportion end fatally and those that do take longer to do so. Probably there are wide regional variations.

Sanatorium waiting-lists offer only a minimal figure. The waiting period is now so long that at many chest clinics the names of patients are just not put on these lists. Domiciliary

treatment is employed as an alternative, often with very good results, but often with the production of further cases by infection in the home, the statistical effects of which will no doubt become apparent in due course. Meanwhile sanatorium physicians, trying to help the general situation by accelerating their turnover, discharge their patients earlier than they would wish, with results less good than we might hope.

Our true aim therefore should be to provide institutional treatment for all cases of active tuberculosis and for cases where activity is suspected for periods long enough reasonably to ensure stability of the lesion. I suggest that, whereas two and a half beds per annual death may serve as an immediate objective, the proper figure may lie, as Bogen (*American Review of Tuberculosis*, 1949, **59**, 707) indicates, somewhere between 5 and 10.—I am, etc.,

Slough, Bucks. BRIAN THOMPSON.

Multiple Primary Carcinoma

SIR,—In view of the recent correspondence (July 29, p. 297) on double synchronous carcinomata we would like to record the following case.

A married woman of 34 was seen in the out-patient department complaining of bilateral mastitic swellings of six months' duration and intermittent abdominal distension. On examination the patient was emaciated and anaemic (Hb 30%). There was a firm swelling 3 in. by 2 in. (5 cm. by 7.6 cm.) occupying nearly the whole of the right breast, not attached to skin or the pectoral fascia. A swelling 1 in. by 1 in. (2.54 cm.) presenting the same physical signs was present in the left breast. There were glands palpable in the right axilla.

The abdomen was distended and a fluid thrill was elicited. Paracentesis withdrew eight pints (4.5 litres) of straw-coloured fluid, and following this a mobile rounded swelling was palpable in the left iliac fossa. She died ten days after admission.

The necropsy revealed a colloid carcinoma of the stomach. The ovaries were replaced by two mobile swellings which proved to be Krukenberg tumours on microscopical section. The right breast on section showed a spheroidal-cell carcinoma, with colloid degeneration in parts of the specimen.

On going into the family history, further interest was added to the case when it was found that the patient's paternal grandfather died of carcinoma of the stomach at the age of 52; her mother died of carcinoma of the stomach at the age of 54; and her father died of a perforated gastric ulcer (pathology unknown) at the age of 51.

This case shows two primary neoplasms and secondaries, with a strong family history of carcinoma of the stomach. The early onset of malignancy in the patient is noteworthy.

We wish to thank Mr. F. P. Forrest for permission to publish this case, and Dr. W. McNaughtan for the pathological reports.

—We are, etc.,

Poole, Dorset. AUSTIN BROWN.
ALEXANDER Z. ELKES.

Genius and Crank

SIR,—Dr. Eliot Slater (July 29, p. 255) overrates the influence which Fliess exerted on Freud. Fliess, whom I knew intimately, never claimed that his own teachings had made a mark on psycho-analysis. Freud's interest in sex was primarily psychologically determined. Breuer and Charcot were his mentors, not Fliess, who was a physiologist trained under Du Bois-Reymond, though he did not share his belief in "Ignorabimus" and was interested in sex from the genetic point of view. Apart from the insight that a homosexual trend is a general tendency in all neurotics, concluded from the Fliessian concept of the *permanent bisexuality* of all living organisms, there is little evidence of Fliess's influence to be found in Freud's writings. This is all the more remarkable as his interest in, and regard for, Fliess, as Dr. Slater rightly states, was very great indeed. When in 1912 I had published a case of hysteria in which the intervals between states of anxiety as well as between appearance and disappearance of conversion symptoms showed the pattern of Fliess's 28-day and 23-day rhythm, and concluded that a periodically recurrent physiological factor precipitates neurotic states, or may even be responsible for psychological mechanisms to be put into action, Freud wrote to me that he would welcome the introduction of this line of investigation into psycho-analytical work. But this was all, and among his disciples no one showed interest in Fliess except Stekel, who, however, no longer belonged to the Freudian school.

It is true that Fliess made it difficult for anyone who did not share Dr. Slater's view that he was a "crank of the first water" to support him. Some of his concepts are and always were untenable. Nevertheless, if one had to prove that he was cranky, one would have to do it on the lines of Dr. Russell Brain's memorable article on "Authors and Psychopaths," and could certainly not mention in evidence teachings which are based on sound observation—e.g., the "bizarre hypothesis of two types of rhythm." This is not a hypothesis. These types exist, as anyone can see who studies one of his books or, for that matter, one of my publications on the subject. The hypothesis which Fliess has built round his observations may be right or wrong or bizarre. But there can be little doubt that they reveal genius. And this fact alone, and not the "emphasis on sexuality," explains Freud's interest in, and high regard for, Fliess. If this were not so, Freud's infatuation (what else could it have been?) would have to be interpreted in psycho-analytical terms.—I am, etc.,

London, N.W.11. B. C. SAALER.

Do Weed-killers Poison Food?

SIR,—Dr. Alan Maberly does a service in his letter published in your issue of July 29 (p. 299) in questioning the assumption that the differential weed-killers and latest insecticides when absorbed into the sap of plants leave no trace in the fruit or seed. The members of these two classes of agricultural and horticultural aids have rendered possible the growth of heavier crops on land already in use and have made it possible to cultivate hitherto unused tracts of tropical countries. However, disturbances in the local oecology are inevitable following their use, and some of these may be undesirable—e.g., the killing of bees, leading to less efficient pollination. (Another trend of modern times is the mechanization of agriculture, leading to the present scarceness of farmyard manure and the consequent increase in the use of artificial manures.) The effect on human teeth of minute amounts of fluorine in water is now well recognized. The use of nitrogen trichloride in the treatment of flour ("agene" process) is to be replaced by the use of chlorine dioxide on the recommendation of the Medical Research Council, not because any effects in humans have been traced to its use but because dogs fed on such treated flour have developed canine hysteria. Is it not possible that such poisonous substances as dinitro-ortho-cresol mentioned by Dr. Maberly may be equally undesirable? O.M.P.A. (octamethyl pyrophosphoramide), which acts by inhibiting cholinesterase and thus affects parasympathetic activity, circulates in the sap of a plant for weeks.

I suggest that the effect on food of such potent substances used in agriculture and horticulture could with advantage be studied and reported on by some such body as the Medical Research Council. Such authoritative pronouncements would aid those entrusted with, or advising on, the formulation of a national food policy.—I am, etc.,

Rochester. J. H. WHITTLES.

A Clarification

SIR,—It has been pointed out to me that there is a misleading remark contained in the table of my article "*Bact. coli* D 433 in Cases of Diarrhoea in Adults" (July 22, p. 195). The remark in question is in connexion with Case 3, where the words "(nor with other cases of this series)" appear in the column headed "Contact with Children." This was intended to make clear that this was the only patient who developed diarrhoea *in hospital*, and so far as could be ascertained this patient could not have been infected by the others of the series. The cases of the series occurred in two separate hospitals in widely separated wards, but it is proposed to make this the subject of a future epidemiological study.—I am, etc.,

Glasgow, N. JOHN S. STEVENSON.

A School for Doctors' Children

SIR,—On p. 89 of the *Supplement* to the *British Medical Journal* of August 12 Dr. J. B. Wrathall Rowe pleads for the erection—inferentially at a cost of £120,000 or thereabouts—of a school for medical war orphans and "other children of doctors, particularly doctors serving overseas." On p. 414 of the same issue the 97th annual meeting of the governors of Epsom College is reported, including a statement that the council intends to make an appeal for funds required to make lasting improvements to the buildings. Is it possible that Dr. Rowe has not heard of Epsom College, and of its Foundation which pays for free board and education at Epsom of medical orphan boys and defrays scholarships elsewhere for girl orphans? Does he know that education is provided there strictly at cost price for the sons of all doctors, and that the buildings have an insured value of £250,000? Does he know of the numerous leaving exhibitions for boys intending to enter the medical profession? In a word, would not his ideals—with which I have a lot of sympathy—be best realized by expanding the resources of Epsom College as the most practical method of achieving what he has at heart? The B.M.A. has already a permanent representation on the council of the College, at present by Mr. N. E. Waterfield, F.R.C.S.—I am, etc.,

HENRY ROBINSON,
Deputy Hon. Treasurer,
Royal Medical Foundation of Epsom College.

Tunbridge Wells.

Nervous Yet Unafraid

SIR,—Vast as is the English vocabulary it would, I think, be improved by the invention of a word which would do away with an unfortunate anomaly. The word nervous on the one hand is used for the great miscellany of neurotic illness and on the other for the timid and fearful. But they have nothing in common. The neurotic may be and in fact often is fearless, almost contemptuous of personal danger, and yet the word lumps him together with the craven-hearted. The new word should be quite new, with no associations with the many unsatisfactory synonyms which have tried vainly to deal with the dilemma. A meaningless word with no ethical significance for the neurotic type of nervousness I suggest is *crobly*, adjective or adverb, and *crobliness*, where a substantive is needed. No such word exists in the *O.E.D.*—I am, etc.,

E. GALLOP.

London, S.W.1.

POINTS FROM LETTERS

Psoriasis

Dr. C. F. PATTERSON (St. Neots, Hunts) writes: I have found that the strain of responsibility and the "adrenal flood" of anger are the principal precipitating factors, and this is why retirement to bed is of value, but there is really more frictional trauma in bed, particularly to the forearms, than anywhere else. As for Father William, cited by Dr. R. M. B. McKenna in his Refresher Course article (July 22, p. 207), the patient does not need to stand on his head to obtain a scalp like a contour map. He can do this quite simply and absentmindedly by scratching or picking at his head while reading his book in bed (or in an armchair), and the more so if his book is exciting or his newspaper alarming. Repeated baths are not advisable, as they clear the skin of its natural oils—including all its vitamin D. No, for the G.P. the answer remains as follows: to limit the patient to one bath a week, followed by a rub with ung. picis carb. co., and to give him a single dose of 150,000 units of vitamin D (i.e., three tablets of calciferol. fort. *N.F.*) in the *summer*, and to advise him not to live in large smoky towns or misty valley bottoms, and either to take regular phenobarbitone or to avoid anger and responsibility. Bed, or phenobarbitone, or both, should help more in the case of fear and anger than cortisone (when it comes), but how the sympathetic nervous system enters into the problem of psoriasis, as it undoubtedly does, still remains a mystery. At present, I suppose, we are forced back to Selye's target organ theory, but have no real idea as yet how this works.

Smallpox in the Unvaccinated

Dr. H. TUDOR EDMUNDS (Slough, Bucks) writes: I should like to reply to Dr. J. S. Gemmill's letter (July 8, p. 107) and to point out that, while it is impossible to prevent atypical cases of smallpox that may occur in the unvaccinated, it is possible to prevent those cases which are brought about by vaccination. . . .

Obituary

BERNARD J. WARD, F.R.C.S.

Mr. Bernard Ward, formerly the senior surgeon of the Queen Elizabeth Hospital, Birmingham, died at his home in Shelsley Beauchamp on July 30. He was 71 years of age, and his health had been failing for some time.

Bernard Joseph Ward was the son of the late Dr. Joseph Ward, who practised for many years in Birmingham. He received his medical education at Birmingham medical school and the London Hospital. Qualifying in 1902, he obtained his F.R.C.S. in 1905. He held resident posts at the Queen's Hospital, Birmingham, and in London at St. Peter's Hospital for Stone. He became assistant surgeon to the Queen's Hospital in 1907, and an honorary surgeon in 1917. In the first world war he served as a captain in the R.A.M.C. He was later appointed consultant surgeon to the Children's Hospital and to the Birmingham City Police. He served the medical school as lecturer and examiner in surgery. He achieved his greatest reputation in urology and in this field became one of the foremost surgeons in the country. He held office as president of the Section of Urology of the Royal Society of Medicine and was vice-president of the British Association of Urological Surgeons. This last office is commemorated by the Ward Medal, which he presented as an award to mark outstanding work in the field of urology. His own great skill in this field earned for him the confidence of the profession and of the public alike. He was a member of the British Medical Association for forty years. He leaves a widow, a daughter, and two sons: to them his many friends offer their sincere sympathy.

L. T. C. writes: For twenty-five years I had the honour to be Bernard Ward's anaesthetist. In that time and in those circumstances I had the unique opportunity of knowing the man, his strength, his weakness, his virtues, and his faults, and now at the end I can say with a full heart, "He was a great man, a powerful friend, and an outstanding surgeon." In this last capacity he was widely known, and such was the quality of his work that we who worked with him were glad to satisfy his demands—and for his patients he demanded the maximum. I recall that as a very young man about to anaesthetize one of our colleagues I sought his opinion, hoping to give "that little more." His reply I have never forgotten. "That little more, my lad! If that is possible, why do you deny it to my other patients? Doctor A is your patient—that is all you need to remember." The quality of a man may be judged by the stories and legends connected with him. In our teaching school, "Beeje," as we called him, figured in so many and, happily, so humorously. The whole man was known to the comparatively few, and that happy few gave him their complete devotion. How many of his furtive kindnesses to patients and friends do I recall—kindnesses which he would deny with the blustering innocence of a schoolboy caught in the larder. At heart "Beeje" was a countryman; horse, hound, and the trout stream for him spelt happiness. He was a man of impressive physique, essentially a man's man. It is pleasant to recall that on his retirement as senior surgeon his old house-surgeons practising in Birmingham gave him a complimentary dinner.

P. L. DANIEL, F.R.C.S.

Mr. P. L. Daniel, consulting surgeon to Charing Cross Hospital, died suddenly on July 28 at Checkendon, aged 79.

Peter Lewis Daniel was born in Carmarthen in 1871. He studied medicine at Charing Cross Hospital and was associated with that hospital for the whole of his professional life, except for a short period of work in Vienna. He qualified in 1898, and took the F.R.C.S. a year later. The list of the posts he held at Charing Cross is a large one, for in his time specialization was not carried to the lengths it is to-day. In addition to several surgical appointments he was also at one time or another house-physician, assistant demonstrator of anatomy, assistant in the electrical department, pathologist, and curator of the museum. He was also on the staff of the Gordon Hospital for Diseases of the Rectum, of the Metropolitan Hospital, Willesden, and of several smaller hospitals near London. He was medical referee to the Cremation Society. He retired from the staff of Charing Cross Hospital in 1931, but he continued to work at the Gordon Hospital until 1948. During the war he was able to help his old hospital, returning as a surgeon to the evacuated hospital at Ashridge.

Daniel was a man of great good sense and a very sound surgeon. He specialized in rectal and abdominal disorders, but quite early in his career he interested himself in the effects of oral sepsis and was the author of a book, published in 1910, entitled *Arthritis: A Study of the Inflammatory Diseases of Joints.* Old Charing Cross students will remember him as a man of fine character and an excellent practical teacher. He is survived by his wife and son, Dr. P. M. Daniel.

Dr. DOROTHEA JANE MANN died at her home in Nottingham on June 29. The elder daughter of the late Rev. Alexander Mann, she was a student at the University of Edinburgh, where she graduated M.B., Ch.B. in 1921, proceeding M.D. in 1926. She held the posts of assistant medical officer to the V.D. clinic and of medical officer in charge of the mental deficiency department at Nottingham.

G. G. D. writes: Some thirty years ago, when we left Nottingham, our house was taken by a young woman who had just graduated in medicine. She told me she was going to set up in practice for herself. We thought it a brave thing to do and wished her well. On our return some years later we found Dorothea Mann still in the same house, fully established, and one of the best-known and most-esteemed practitioners in the city, with a large general practice, built up by hard work and medical skill. She was just the right person to be a doctor, kindly, generous-minded, full of charm and personality. Her patients adored her, for, beside giving of her best for their ailments, she was interested in them as persons and could advise in their ordinary lives in a wonderfully far-seeing way. A few years ago she had a serious illness which we thought had yielded to treatment, and about which she made light, going on with her work as selflessly as usual. Early this year, however, she realized she was a very sick woman and was persuaded to retire. Within six months the end came. Her loss is irreparable, and it will be a long time before we see her like again.

ELIZABETH HONOR BONE died at her home in Hampshire on July 9 at the age of 75. Owing to ill-health she had led a quiet life since her retirement from general practice in 1935. She was the second of three daughters of William John Bone, manager of the Tyne Iron Shipbuilding Company; the girls were brought up on Tyneside and eventually sent to school in Edinburgh. Later she studied medicine at the Royal Free Hospital and London School of Medicine for Women. She graduated M.B., B.S. in 1898, and proceeded M.D. in 1905. While a student she met the late Dr. Christine Murrell, and together they planned to equip themselves to start general practice in the West End of London in a professional and well-to-do district. Graduates from the school were already established in many varieties of consultant practice, but women general practitioners had usually settled in industrial and working-class districts, so that the plan was something of an innovation for women at the turn of the century. Dr. Bone went to Vienna and Berlin after qualifying, and then took an appointment as medical officer to the Women's Settlement in Liverpool. Here, while practising in the dock areas, she worked with Sir Robert Jones. This contact influenced her outlook in practice very greatly. The partnership planned by Dr. Bone and Dr. Murrell began in 1903 in Bayswater (the first year's takings amounting to £87). The practice grew rapidly and was well established by the beginning of the first world war. Third, fourth, and fifth partners were taken on. Dr. Bone was an ideal family physician. She was a very small person with the quiet gravity which is always reassuring to children. She paid meticulous attention to detail both in diagnosis and treatment, and many of her old patients recall the good years when she ruled the health of their growing families. She had perfected the use of her senses in eliciting physical signs to an unusual extent and had a great gift for training her assistants. She was a part-time school medical officer under the L.C.C. for some years and was one of the original medical officers at the North Kensington Baby Clinic before infant-welfare centres were established. Here she had full opportunity for the constructive paediatric work that was dearest to her. Her small stature and her wish for a quiet life with no public appearance of any sort were in striking contrast to the imposing figure and full public activity of her partner, Christine Murrell, but the association of these two doctors in practice for 30 years had the happiness which so often results from wide dissimilarities.—A. G.

Dr. EDWARD MOIR, who had been senior anaesthetist to the Manchester Royal Infirmary for many years, died suddenly at his home in Combs, Chapel-en-le-Frith, on July 25 at the age of 72. The son of the late Dr. Douglas Moir, he qualified in 1907 and obtained his D.A. at Manchester in 1939. In addition to his appointment as anaesthetist to the Manchester Royal Infirmary, he was on the staff of the Manchester Ear Hospital and the Macclesfield Infirmary. F. G. W. writes: Edward Moir was for many years one of Manchester's foremost anaesthetists. His proficiency in his specialty was well recognized among his surgical colleagues, and his services were in great demand, particularly with ear-nose-and-throat surgeons. He could give a difficult anaesthetic for a bronchoscopy or an oesophagoscopy as well as anybody, and a great deal better than most. He was one of the old school to whom chloroform was the ideal anaesthetic, and in his hands it certainly proved a very safe and effective drug. Moir was always kind to his patients, especially to children, with whom he would carry on a conversation during the induction period; this was of course before the days of premedication. To his colleagues he was courteous and most obliging in every way. The regularity of his attendance in his hospital work was exemplary, and he would never think twice about going to hospital for urgent work at any time of the day or night. Dr. Moir's other sphere was that of athletics. In his student days he first played "soccer" for the university, but soon transferred his affection to "rugger." He remained faithful to the latter game for the rest of his life, both as a player and later in an advisory capacity. He was vice-president of the Manchester University R.C. and president in 1911, and again from 1922 to 1926. He was life president of the University Athletic Club, and president of the Athletic Union in 1919 and 1920. Moir was an official starter at the University Athletic Ground, and his capacity was recognized by his appointment as starter to the Olympic Games at Paris in 1924 and at Amsterdam in 1928. He served as a representative on the Lancashire and English Rugby Unions, where his experience and knowledge were of great value. His loss will be felt not only in the medical world but also in the field of athletics, where he was a well-known and popular figure.

Dr. ERNEST SOLLY, of Harrogate, died on July 26 at the age of 87. He was educated at Rugby School and studied medicine at St. Thomas's Hospital. He qualified in 1886, graduated M.B. in 1887, and took the F.R.C.S. a year later. After a period as a resident at the Royal Free Hospital, he came to Harrogate in 1893, taking over the practice of the late Dr. Russell. He began as a general practitioner and spa physician. Later he specialized in surgery and was appointed surgeon to the Harrogate Hospital in 1905, a post which he held up to 1932, when he retired to the consulting staff. He was also honorary surgeon to the Yorkshire Home for Incurables and Chronic Diseases. As a surgeon he was deft with his fingers, meticulous in procedure, and of sound judgment. He took an early interest in municipal affairs, serving on the town council for nine years, and becoming mayor in 1898. His work during these years as liaison officer between the corporation and the medical profession was invaluable, for he took an active part in the development of the spa. He served in France during the 1914–18 war in the R.A.M.C., attaining the rank of major. Mr. Solly had been a member of the British Medical Association for 50 years. He was a vice-president of the Section of Dermatology in 1906 (when the Association met at Toronto); a member of the Central Ethical Committee from 1932 to 1939; and represented his constituency at the Annual Representative Meetings in 1905, 1926, 1928, 1929, 1930, and 1932–9. Apart from his profession he had wide interests. Philately was his chief hobby; he had a large and valuable collection of stamps. At carpentry he was an adept. In his earlier years he was a keen cricketer, and he took an active part in the development of the Boy Scout organization. He was a founder member of the Harrogate Rotary Club. A man of many parts, he was well read and had a good memory. His general knowledge was great. When called upon he could deliver an interesting address on almost any subject desired. Of late years he led a retired life owing to failing health. His wife died in 1932. He is survived by one son and three daughters; another daughter died in 1946. He will be greatly missed by all his contemporaries and friends.

Dr. JOHN HERBERT BANKES, of Lindfield, Sussex, died on August 1 in London, aged 71. He was related to the well-known family of lawyers and judges of that name. He was a student at St. George's Hospital, and he qualified in 1904. Afterwards he practised in South Kensington. He served in the R.A.M.C. during the 1914–18 war, and on demobilization did not resume general practice but took an appointment with the Ministry of Pensions. In this he was so energetic and successful that in 1929 his name was put forward for appointment as deputy lieutenant for the County of London, and he was duly chosen. Throughout his career Dr. Bankes was a keen Mason. He was Provincial Grand Master for the Province of Middlesex, and he was on the boards of management of both the masonic educational charities. He had lived in (professional) retirement for several years, but always came to London for meetings of the lieutenancy and for his masonic duties.—H. R.

The Services

Surgeon Captain G. F. Abercrombie, V.R.D., R.N.V.R., has been appointed an Honorary Physician to the King in succession to Surgeon Captain C. C. Elliott, D.S.C., V.R.D., R.N.V.R.

A *Supplement* to the *London Gazette* has announced the following awards:

"1st Clasp" to the Territorial Efficiency Decoration.—Lieutenant-Colonel S. W. Barber, M.B.E., T.D., R.A.M.C.

Territorial Efficiency Decoration and "1st Clasp."—Major (Honorary Lieutenant-Colonel) C. L. Heanley and Majors J. E. Elliott and P. H. Jobson, R.A.M.C.

Territorial Efficiency Decoration.—Majors S. Curwen and R. F. Ward (died by enemy action), Captains (Honorary Majors) F. D. Hindmarsh, A. D. Kelly, M.B.E., A. J. G. Newton, and J. M. Sturrock, Captains C. F. Fairlie and S. Howe, R.A.M.C., and Captain E. Saunsbury, T.A.R.O., R.A.M.C.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Frank Howarth, M.D., has been appointed a University Lecturer in Pharmacology with tenure for three years from October 1.

Nigel Dean Compston, M.D., has been elected to the E. G. Fearnsides Scholarship.

UNIVERSITY OF EDINBURGH

At a graduation ceremonial on July 19 the following degrees and diplomas were conferred:

M.D.—[3] [5]D. M. Blair, [3]H. M. Brown, [4]J. H. F. Brotherton, [5]J. Collins, Mary A. J. T. Douglas, Frances M. Earle, Audrey L. Ferguson, [2]D. C. Haig, S. P. Hall-Smith, Morag L. Insley (née Henderson), [2]Mary E. Lothian (née McLaren), [1]I. F. Sommerville, [2]T. Sommerville, [3]J. A. Tulloch, [2]J. Wallace, [1]G. M. Wilson.

D.Sc.—*In the Department of Pure Science:* R. F. Ogilvie, M.D.

PH.D.—*In the Faculty of Medicine:* F. H. Sims, M.Sc., M.B., Ch.B.

M.B., CH.B.—J. G. Abercrombie, W. T. C. Adamson, A. A. Akiwumi, D. S. Alexander, Jean M. Arkieson, Natalie H. F. Armstrong, J. D. Arthur, T. A. Ballingall, Rosemary A. Begg (née Kemp), Sheila M. Black, Jennifer P. Bland, R. Bliss, D. W. Bookless, Elizabeth S. Brown (née Bennett), J. R. Brown, L. S. Brown, Janet C. Bryce, Patricia M. Burke, I. D. Campbell, J. C. Cape, R. A. Caulfield, J. Chalmers, I. MacD. Clark, I. L. Clark, Agnes A. Cochrane, J. F. J. Collins, I. A. Colville, N. M. J. Cowan, F. J. Darby, A. H. Darling, A. S. Dawson, R. McN. Dean, I. Dial, G. M. Dobbie, C. G. B. Downie, R. W. Downie, J. J. Drever, Catherine W. Drysdale, R. Edmond, A. E. Elliott, D. J. Erskine, G. S. Fiddler, J. W. Fisk, J. I. McL. Forsyth, G. D. Forwell, Margaret C. Galloway, W. A. S. George, J. M. C. Gibson, Deidre M. M. Gillies, Elsie M. Glennie, T. M. Goodall, A. B. Goorney, J. G. Gray, G. J. Green, D. C. Greig, S. C. C. Grieve, R. E. Gristwood, A. A. Gunn, G. K. M. Hall, A. M. Hall-Gardiner, W. A. Hanna, J. Harkness, Joan Harper-Ball, D. M. Hastings, R. E. Haworth, Daphne E. A. Healey, Ethna E. R. Henderson, Jean M. Higgins, J. Hill, G. F. A. Howie, R. Hutchinson, Margaret Jackson, F. D. Johnston, W. T. Jones, Victoria K. Kelly, D. S. S. Ker, C. O. R. King, [4]M. R. King, J. R. Kirkpatrick, A. W. Laing, [4]Anne T. Lambie, I. H. Lawrence, Barbara Leach, F. H. Lockwood, J. R. A. Luckas, R. McAdam, J. S. McP. Macaskill, R. H. McClure, P. W. McCormick, F. I. MacDonald, J. D. McDonald, J. S. Macdonald, Jill MacDonald (née Russell), Annie McL. McDougall, J. B. Macfarlane, P. S. MacGibbon, A. D. McIntyre, Patricia C. Mackay, G. L. MacLeod, D. C. McNutt, A. I. MacPhail, Margery A. Macpherson, Frances E. A. McVey, D. H. McVie, W. L. Marshall, J. A. McL. Martin, M. C. Maw, A. W. Maxwell, D. Maxwell, N. Mendick, G. L. Minter, Jean S. H. Mitchell, L. Mitchell, Pamela A. Moncrieff, B. McL. More, Donalda M. Morgan, J. A. L. Morrell, Hilary L. Morss, Mary W. Moss, J. R. Munro, Danuta Oktawiec, L. L. Ostrowski, I. V. E. Owen, J. C. Paterson, Joan Pears, D. Penman, W. A. Penman, N. B. Peterkin, A. F. Phillips, J. T. Rabie, B. A. Rapier, I. D. Reid, L. R. Roberts, J. G. Robertson, Elizabeth Rose, W. R. Ross, [4]G. F. M. Russell, I. A. Ruthven-Stuart, J. D. St. Clair, T. F. Sandeman, P. J. Scally, D. G. Scott, G. A. Scott, R. G. Scott, Kathleen J. C. Shaw, W. C. Shepherd, F. O. Simpson, W. T. Simpson, [4]A. W. McI. Smith, S. McC. Smith, Yvonne R. Sneddon, J. Spence, J. F. Stephen, W. I. Stuart, Pamela M. Sutherland, Elizabeth M. Sweet, Margaret E. Taylor, W. Taylor, B. Teelock, A. Thomson, W. G. Thomson, Priscilla E. Turnbull, D. H. Vaughan, Margaret A. Walker, W. C. Walker, W. G. Walker, J. J. Wallace, A. S. Watson, Alison A. P. Watson, A. St. J. Wilding, A. K. Wilson, G. C. Wilson, Pauline I. M. Winn, H. J. Woodliff, D. G. Wray, A. C. Wright, M. J. Wright, Sheena M. Yule.

B.Sc.—*In the Department of Pure Science:* P. N. Edmunds, M.B., Ch.B. (with first-class honours in bacteriology).

D.P.H.—M. D. B. Ahmad, A. McD. Allan, Doris M. Beaton, G. Dison, G. A. F. R. Gibson, R. Lwin, Phyllis E. Lyne, Joan M. McWilliam, J. McE. Neilson, C. A. Phillips, I. C. Wilson.

D.T.M.&H.—W. L. Barton, A. R. Duff, A. B. G. Laing, G. S. C. Nzegwu, W. T. Thom, A. V. Wells.

D.M.R.D.—R. J. Bruce, M. A. Caldwell-Nichols, R. Cuthbert, J. G. Duncan, G. Goodhall-Copestake.

D.M.R.T.—V. R. Naidu.

DIPLOMA IN PSYCHIATRY.—Helen C. S. MacLean.

The Cameron Prize in Practical Therapeutics has been awarded to Rudolph Albert Peters, M.D., F.R.S., Whitley Professor of Biochemistry in the University of Oxford and Fellow of Trinity College, Oxford, in recognition of his discovery of British anti-lewisite (B.A.L.) and the application of this drug in practical therapeutics.

The following scholarships, bursaries, prizes, etc., were also awarded in the Faculty of Medicine. *Ettles Scholarship and Leslie Medal, Scottish Association for Medical Education of Women Prize, Dorothy Gilfillan Memorial Prize,* and *Lawson Gifford Prize in Obstetrics and Gynaecology,* Anne T. Lambie. *Buchanan Scholarship in Obstetrics and Gynaecology,* A. W. McI. Smith. *James Scott Scholarship in Obstetrics and Gynaecology,* J. D. St. Clair. *Mouat Scholarship in the Practice of Physic,* G. F. M. Russell. *Beaney Prize in Anatomy and Surgery, Annandale Medal in Clinical Surgery,* and *Keith Memorial Prize in Systematic Surgery,* M. R. King. *Murdoch Brown Medal in Clinical Medicine,* F. O. Simpson. *Royal Victoria Hospital Tuberculosis Trust Medal,* Kathleen J. C. Shaw. *Wightman Prize in Clinical Medicine,* G. F. A. Howie. *Sir Robert Jones Prize in Orthopaedic Surgery,* I. A. Ruthven-Stuart. *Vans Dunlop Scholarship in Materia Medica and Medicine,* C. W. M. Wilson. *Gunning Victoria Jubilee Prize in the Practice of Physic,* Constance C. Forsyth. *Gunning Victoria Jubilee Prize in Chemistry,* A. B. Roy. *Thomson Memorial Medal in Child Life and Health,* Margaret J. Poole. *Stirton Bursary* and *Colonel Thomas Biggam Memorial Medal and Prize in Pathology,* S. H. Davies. *Maclagan Prize in Forensic Medicine,* K. Wood. *Wellcome Medal and Prize in the History of Medicine,* H. P. Tait. *Junior John Aitken Carlyle Bursary in Anatomy and Chemistry,* P. H. Jaques. *Whiteside Bruce Bursary,* J. C. J. Ll. Bath. *Mackenzie Bursaries,* H. A. Crispin, Mary G. Dunlop, Dorothy L. Grieve, C. M. Taylor. *Robert Wilson Memorial Prize in Chemistry,* W. C. Hartley. *Vans Dunlop Prize in Physics and Chemistry,* J. C. J. Ll. Bath and W. C. Hartley (equal). *Vans Dunlop Prize in Botany and Zoology,* Elizabeth M. Connell and Elizabeth L. Handasyde (equal). *MacGillivray Prize in Zoology,* Elizabeth M. Connell.

[1]Awarded medal for thesis. [2]Highly commended for thesis. [3]Commended for thesis. [4]With honours. [5]In absentia.

UNIVERSITY OF LONDON

Frederick Murgatroyd, M.D., F.R.C.P., has been appointed to the Wellcome Chair of Clinical Tropical Medicine, tenable at the London School of Hygiene and Tropical Medicine, from October 1.

Stephen Dyonis Elek, M.D., Ph.D., has been appointed to the University Readership in Bacteriology, tenable at St. George's Hospital Medical School, from October 1.

Bernhard Katz, M.D., Ph.D., D.Sc., has been appointed to the University Readership in Physiology, tenable at University College, as from October 1.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

The following candidates were duly admitted Licentiates in Medicine and Midwifery on July 7, having passed the final examination in Medicine, Surgery, and Midwifery of the Conjoint Board of Ireland: J. C. C. Ryan, Louise Burleigh, Bridget Conlon, Norma A. C. Coogan, J. O. MacC. Craig, Margaret J. E. Dickinson, B. M. Gray, A. D. Kelly, J. A. Lagan, Eileen P. Leahy, E. W. A. Malone, Nora J. Murphy, Eibhlin M. MacCollum, D. F. McFeely, L. E. McLoughlin, Fiona M. O'Brien, R. V. Power, A. I. Roith, J. B. Sheils, Nualla P. Summerville, O. G. Tolkin, Maura V. Toner, F. P. Treacy, J. H. Walsh, A. E. O. Williams, P. J. Yoffe.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the Royal College of Obstetricians and Gynaecologists, held in the College House on July 22, with the President, Professor Hilda Lloyd, in the chair, the following officers were re-elected: *President,* Professor Hilda Nora Lloyd; *Vice-presidents,* Mr. John Eric Stacey and Dr. V. B. Green-Armytage; *Honorary Treasurer,* Mr. Arthur A. Gemmell; *Honorary Secretary,* Mr. Humphrey G. E. Arthure; *Honorary Librarian,* Mr. Frederick W. Roques; *Honorary Curator of the Museum,* Mr. Aleck W. Bourne.

The following candidates were elected to the Membership of the College: G. T. Altimas, J. D. Andrew, P. R. Blahey, G. T. Carson, C. J. Champ, F. L. Clark, T. R. Clarke, W. W. Coppinger, B. M. Corkill, E. D. Crichton, C. N. Degaris, W. Donovan, H. P. Dunn, Isabel L. Dyke, M. W. Elliott, B. Fatima, C. J. Farr, W. R. Foote, M. B. Fox, H. H. Francis, A. C. G. Frost, W. D. Giffen, C. A. Haxton, H. A. Henderson, H. F. Hills, R. Hodkinson, R. H. Horner, D. R. Hughes, T. G. Ingram, D. J. McI. Irvine, H. A. Kelsey, D. Kutty, J. F. Leaver, J. L. MacArthur, D. C. McEwen, K. T. MacFarlane, Ishbel M. Macrae, C. M. Mair, W. D. Marshall, G. B. Maughan, A. C. Naylor, Helen M. Noble, R. H. O'Hanlon, D. C. P. Paranjothy, M. G. Pearson, E. Quehl, G. J. Quigley, P. D. Rajaratnam, I. Ramamurthi, D. H. Rea, K. E. E. Read, H. A. Rowley, A. M. Rutherford, D. R. Sheumack, J. M. Slattery, E. M. Southern, D. W. Sparling, S. K. S. Roy, L. G. R. Van Dongen, D. B. B. Whitehouse, J. Wilbush, E. A. Williams, M. H. V. Young.

No. 30

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended July 29.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each Infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1950 (a)	(b)	(c)	(d)	(e)	1949 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Meningococcal infections	28	2	14	1	3	28	1	10	—	2
Deaths		—	—				2	—		
Diphtheria	42	2	6	4	2	76	12	24	8	1
Deaths	—	—	—	—	—	—	—	1	—	—
Dysentery	166	7	83	—	—	90	6	54	1	—
Deaths		—			—				—	—
Encephalitis, acute	6	—	—		—	3	—	1	1	—
Deaths		—		—			—			
Erysipelas			16	2	1			17	10	4
Deaths							—			
Infective enteritis or diarrhoea under 2 years				35					53	
Deaths	6		3	—	—	31	4	3	4	3
Measles*	8,291	580	158	151	92	5,052	379	92	140	64
Deaths†		—	1	—	—			—	1	—
Ophthalmia neonatorum	24	—	11	—	—	37	4	11	1	—
Deaths										
Paratyphoid fever	7	1	—	5(B)	—	54	—	9(B)	—	—
Deaths	—		—		—	—	—	—	—	—
Pneumonia, influenzal	277	14	2	—	1	329	16	1	5	8
Deaths (from influenza)‡	3	—	—	1	—	10	2	—	—	—
Pneumonia, primary			112	¶				114	17	
Deaths	97	18		3	2	129	23		5	7
Poliomyelitis, acute	305	25	52	2	15	99	7	7	1	—
Deaths§	17	2		—		6	1			
Puerperal fever		—	5				—	5		
Deaths										
Puerperal pyrexia‖	87	13	5	—	2	95	12	9	—	2
Deaths							—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,012	73	114	61	57	1,157	91	89	74	31
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	10	—	—	1	—	8	—	3	3	—
Deaths	—	—	—		—	—	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Whooping-cough	3,714	268	297	63	34	2,004	86	29	54	82
Deaths	8	—	1	—	—	3	—	—	1	1
Deaths (0–1 year)	194	14	27	14	8	254	33	30	18	15
Deaths (excluding stillbirths)	3,917	572	478	127	98	3,926	659	530	154	112
Annual death rate (per 1,000 persons living)			9·6					10·6	9·5	
Live births	6,963	1118	817	387	219	7,295	1225	980	401	
Annual rate per 1,000 persons living			16·4					19·7	24·8	
Stillbirths	173	13	18			152	24	28		
Rate per 1,000 total births (including stillborn)			22					28		

* Measles is not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

¶ Primary pneumonia no longer notifiable in Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

Notifications of poliomyelitis in the week ending August 5 were: paralytic 262 (197); non-paralytic 105 (108); total 367 (305). The figures for the previous week are shown in parentheses. The following county areas, with notifications as given, contributed some 69% of the total notifications for England and Wales in the week under review:

	Paralytic	Non-paralytic
London	16	12
Essex	14	3
Gloucester	6	5
Lancaster	15	7
Middlesex	8	3
Northumberland	8	6
Southampton	8	3
Stafford	21	12
Surrey	10	2
Warwick	24	14
Worcester	21	5
Yorks (West Riding)	18	6

The total increase for the week of 62 compared with the previous week was due to increases in notifications in a number of counties, of which the more important were Hertford, Kent, Lancaster, Lincoln (Holland, Kesteven, and Lindsey), Northumberland, Stafford, Surrey, Worcester, Yorkshire (West Riding). Notifications of non-paralytic cases dropped to 29% of the total compared with 35.4% in the preceding week.

Cases notified in the Isle of Wight in the week ended August 5 were paralytic 4, non-paralytic 3. Numbers have increased since that to a total of 28 confirmed cases (including 26 paralytic) by August 12. The medical officer of health has advised that visitors with children should not visit Freshwater and Newport for the time being.

According to the *Weekly Epidemiological Record* of August 2 of the World Health Organization, the following is a summary of the situation in countries other than Britain where a relatively high incidence of poliomyelitis is reported for 1950:

Australia.—Epidemic outbreaks occurred in 1949, and the incidence is still high in 1950. The number of cases has been decreasing since the week ending June 17, when 207 cases were reported. The figure fell to 116 during the week ending July 8. Corresponding figures for 1949 are 66 and 60.

United States.—The incidence is high, but not so high as last year at the same time. For the week ending July 15, 665 cases were reported, as against 1,014 in 1949. Total cases registered in the U.S.A. since January 1 number 4,328, against 4,883 for the corresponding period of 1949.

Germany.—There has been an increase of cases during recent weeks in the German Federal Republic. Whereas 41 cases had been reported during the week ending June 17, the number rose to 51 during the week ending July 8. The incidence in the corresponding weeks of 1949 had been 10 and 16 respectively.

Belgian Congo.—Poliomyelitis notifications in the Belgian Congo, which until 1947 had never been more than 53 per year (in 1936), rose to 111 in 1948 and 207 in 1949. This year 38 cases were reported for the week ending July 8, against 9 for the corresponding period of 1949 and 0 for the same week in 1948.

France.—The number of cases recorded from January 1 to July 15 is higher than that of the corresponding period during the years 1942–9: 519 in 1950 against 296 in 1949. Last year's incidence (1,957 cases) was the greatest for two decades.

Mexico.—During the period May 21–June 17, 53 cases were reported in the Federal District. In 1949 the May and June incidence in all Mexico was 18 and 32 respectively.

Philippines.—The number of cases of poliomyelitis reported at Manila is considerably higher in 1950 than during the preceding years. Up to July 8, 117 cases were reported, whereas the annual incidence in the years since 1939 never exceeded 63. For the week ending July 8, 32 cases were reported, against 0 for the corresponding period in 1949.

Discussion of Table

In *England and Wales* there were decreases in the notifications of measles 463, whooping-cough 167, and scarlet fever 141. The number of notifications of dysentery was the same, 166. The number of notifications of acute poliomyelitis (305) was 45 more than in the previous week.

In *Scotland* there was a decrease in the notifications of dysentery 26, while there were increases in the notifications of whooping-cough 92 and scarlet fever 16. There was a decrease in the number of notifications of acute poliomyelitis from 58 in the previous week to 52.

In *Eire* there were decreases in the notifications of measles 78 and whooping-cough 23. The notifications of scarlet fever increased by 8 to 61.

In *Northern Ireland* there were increases in the notifications of measles 17, whooping-cough 11, and scarlet fever 7. There were 15 cases of acute poliomyelitis notified, three fewer than the previous week.

Week Ending August 5

The notifications of infectious diseases in England and Wales during the week included scarlet fever 956, whooping-cough 3,687, diphtheria 45, measles 7,973, acute pneumonia 273, acute poliomyelitis 367, dysentery 179, paratyphoid 5, typhoid fever 8.

Medical News

Birth of a Princess

The following bulletin was issued from Clarence House on Tuesday, August 15: "Her Royal Highness Princess Elizabeth, Duchess of Edinburgh, was safely delivered of a princess at 11.50 a.m. to-day. Her Royal Highness and her daughter are both doing well." The bulletin was signed by Sir William Gilliatt, Mr. John H. Peel, Dr. V. F. Hall, and Sir John Weir.

Harveian Society at Papworth

The summer meeting of the Harveian Society of London was held in the Papworth Village Settlement on July 19. Members and their guests were entertained to lunch, after which Dr. R. R. Trail, the president of the Society and medical director of the Settlement, explained the principles on which Papworth worked. The three main principles were active treatment, rehabilitation, and resettlement. During the 32 years of its existence no child born at Papworth had developed pulmonary tuberculosis, and even those men from Papworth who were prisoners of war in Japanese hands in the recent war had not developed pulmonary tuberculosis as the result of their captivity. A visit was paid to the *x*-ray department, where demonstrations of cases were given. The industries were subsequently visited, and patients were seen at work making leather goods, furniture, and motor-car bodies, or engaged in printing and bookbinding. Dr. Hope Gosse proposed a vote of thanks to the committee of management for extending the invitation and to Dr. Trail and Miss Robinson, the matron.

Records of the Fallen

The R.A.M.C. War Memorial Fund has now issued a booklet entitled "The Book of Remembrance," which gives the roll of honour of the 437 officers and 2,026 N.C.O.s and men of the Corps who gave their lives in the 1939–45 war. In addition, it records the ceremony on June 27 in Westminster Abbey last year, when the original of the roll was placed beside the Golden Book which gives the names of the 743 officers and 6,130 other ranks who died in 1914–18. Both books are now housed in the Pyx Chamber of the Abbey.

History of Science

The *British Journal for the Philosophy of Science*, which began publication in May, is sponsored by the Philosophy of Science Group of the British Society for the History of Science. Its aim is to direct attention to the philosophical basis of the sciences, and it will deal among other things with problems of logic and methodology and the interrelation between the sciences. The journal will be published quarterly by Thomas Nelson and Sons at an annual subscription of 30s.

Health Services for Children

A committee convened by the World Health Organization has met to recommend measures designed to improve health services for children of the school-age group. Dr. Fraser C. Brockington, medical officer of health of Yorkshire West Riding, was elected chairman, and Professor Jacob de Haas, from The Hague, was elected vice-chairman. Among the problems discussed were the nutritional aspects of school health, preventive mental-health education, and medical supervision in schools.

Editor of Tuberculosis Journal

Dr. Philip Ellman is succeeding Dr. Clifford Hoyle in the editorship of the *British Journal of Tuberculosis and Diseases of the Chest*. He will be assisted by an editorial board which comprises Dr. Clifford Hoyle, Mr. T. Holmes Sellors, Dr. A. Brian Taylor, and Professor Cameron. Dr. Clifford Hoyle succeeded the late Dr. L. S. T. Burrell in 1938 and has edited the journal for 12 years.

New Members of M.R.C.

Professor W. E. le Gros Clark, F.R.S., professor of anatomy in the University of Oxford, and Professor F. G. Young, F.R.S., professor of biochemistry in the University of Cambridge, have been appointed members of the Medical Research Council from October 1.

Wills

Professor John Alfred Ryle, professor of social medicine in the University of Oxford, and formerly regius professor of physic at Cambridge, left £27,608. Dr. Bertram Henzell Pidcock, of Winchester, left £18,517; Dr. Harry Bowen Williams, of Goring by Sea, £11,922, bequeathing £500 to the Royal Medical Benevolent Fund.

COMING EVENTS

London Nursing Exhibition

The London Nursing Exhibition will be held at Seymour Hall, Seymour Place, London, W.1, on October 23–27 concurrently with the Professional Nurses and Midwives Conference. Information may be obtained from the organizer at the *Nursing Mirror*, Dorset House, Stamford Street, London, S.E.1.

International Society of Medical Hydrology

A meeting of the International Society of Medical Hydrology will be held in Florence, Italy, from October 3 to 7. The subjects under discussion will be "Sweat," on October 4, and "Gout," on October 5. Members of the medical profession who wish to attend the meeting should communicate with Dr. Donald Wilson, "Cranbourne," Southdown Road, Bognor Regis, Sussex.

Bengué Memorial Award Lecture

Dr. Nadia du Bouchet, head of the Anaesthetic Centre and chief instructor of the Teaching Centre, Broussais Hospital, Paris, will deliver the Bengué Memorial Award Lecture on "Modern Anaesthesia in France and its Developments related to Cardiac Surgery" at the Royal Institute of Public Health and Hygiene, 28, Portland Place, London, W., on Wednesday, September 20, at 3 p.m. Admission to the lecture is free, without ticket, but applications for seat reservations may be made to the secretary of the institute.

London County Medical Society

The next clinical meeting of the London County Medical Society will be held at St. Stephen's Hospital, Fulham Road, Chelsea, S.W., on Thursday, September 14, at 3 p.m. All inquiries and communications should be made to Mr. J. Gabe, F.R.C.S., St. Alfege's Hospital, Greenwich, S.E.10 (Tel.: Greenwich 2655, Ext. 48).

British Postgraduate Medical Federation

The British Postgraduate Medical Federation has arranged a course of lectures on "The Scientific Basis of Medicine" to be given at the London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., on Tuesdays and Thursdays, at 5.30 p.m., from October 10 to March 20, 1951. The lectures are designed especially for research workers and specialists in training, and admission is free without ticket. Details will be published in the diary column week by week.

Malcolm Morris Memorial Lecture

Professor J. Earle Moore, M.D., of Johns Hopkins University, Baltimore, U.S.A., will deliver the Malcolm Morris Memorial Lecture under the auspices of the Chadwick Trust at St. Mary's Hospital Medical School, Norfolk Place, Praed Street, Paddington, London, W., on Thursday, September 21, at 4.30 p.m. His subject is "The Public Health Aspects of Venereal Disease Control." Admission to the lecture is free and no tickets are required.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Wednesday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, August 23, 3.30 p.m., "*Endocrine Control of Carbohydrate Metabolism*," by Professor F. G. Young, F.R.S.

APPOINTMENTS

Dr. Edward John Bury has been appointed an Appointed Member of the Executive Council of the Gambia.

AFFLECK, IAN, O.B.E., M.R.C.S., L.R.C.P., Factory Doctor for Farnworth, Lancs.

BREARLEY, BRIAN F., M.B., B.Chir., M.R.C.P., Consultant General Physician, Preston and Chorley Hospitals.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—*Senior Registrar in Radiology at White Lodge Hospital, Newmarket*, K. E. Barlow, M.R.C.S., L.R.C.P., D.M.R. *Consultant Psychiatrist at St. Andrew's Hospital, Thorpe, Norwich*, J. D. Fraser, M.D., D.P.M.

HUTCHISON, ALEXANDER, M.D., Ph.D., F.R.F.P.S., D.P.H., D.P.A., Medical Officer of Health and School Medical Officer, Bolton.

JONES, M. T. ISLWYN, M.D., D.P.H., County Medical Officer of Health and School Medical Officer, Denbighshire.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Baker.—On August 9, 1950, at Wednesbury, Staffs, to Hazel Baker, M.B., B.S. (formerly Hill), wife of Mr. T. A. C. Baker, M.A., a son—Robert Frederick.

Smillie.—On July 25, 1950, to Pamela (formerly Stevens), wife of Dr. T. G. Smillie, 195, Greenhill Avenue, Sheffield, 8, a son.

MARRIAGE

Forbes—Burbery.—On August 5, 1950, at Newton Abbot, John Ronald Forbes, M.D., to Pamela Stone Burbery, S.R.N.

DEATHS

Brand.—On August 7, 1950, at St. Andrews, William Gillon Brand, M.B., Ch.B., of 3, Elms Avenue, Lytham St. Annes, Lancs, formerly of Adlington, near Chorley.

Brims.—On July 31, 1950, Donald James Brims, M.R.C.S., L.R.C.P., of 8, Devonshire Place, London, W.

Craig.—On August 8, 1950, in Scotland, Douglas Craig, M.D., of Stanford-le-Hope, Essex.

Ferguson.—On August 3, 1950, at Hillcrest, Bodorgan Road, Bournemouth, James Henry Ferguson, M.R.C.S., L.R.C.P.

Hunter.—On July 29, 1950, at Nairobi, Ernest Villiers Hunter, L.M.S., of the C.M.S., Uganda, aged 73.

Jensen.—On July 30, 1950, at 25, Berkeley Square, London, W., Ernest Thomas Jensen, M.B., aged 76.

Lornie.—On August 8, 1950, at 7, Barossa Place, Perth, Peter Lornie, O.B.E., M.D., aged 68.

Morris.—On August 3, 1950, at Lew Down, Devon, Henry Gibbins Morris, M.R.C.S., L.R.C.P.

Oxley.—On July 30, 1950, Frederick John Oxley, O.B.E., T.D., M.R.C.S., L.R.C.P., of 66, Palmerston Road, Buckhurst Hill, Essex, aged 83.

Steele.—On August 9, 1950, in a nursing-home, William Frederick Steele, M.B., B.S., of 32, Severas Avenue, Acomb, Yorks, late of Tockwith and Darwin, Lancs.

West.—On July 29, 1950, at Hazelcombe, Dulverton, Somerset, Waldemar Shipley West, M.D., formerly of Aylesbury, aged 84.

Young.—On August 12, 1950, at 8, Ampton Road, Edgbaston, Birmingham, James Carruthers Young, M.C., M.D., M.S.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Intravenous Procaine in Asthma

Q.—*I understand that in the U.S.A. intravenous procaine ½% has been used in the treatment of asthma. I have tried it on two occasions—giving 5 ml. intravenously—in status asthmaticus which had not responded to any familiar treatment. In both cases complete relief of the bronchial spasm resulted within half an hour. Is there any literature on this treatment, particularly on dosage, side-effects, dangers, contra-indications, etc.?*

A.—Intravenous procaine is recognized as a method of treating status asthmaticus both in America and in this country. Intravenous procaine has chiefly been used by the anaesthetists, and many of the references concerning its use are in the journals devoted to this specialty. A review by W. W. Mushin and L. Rendell-Baker on the uses of intravenous procaine (*Lancet*, April 9, p. 619) refers to its effect on allergic conditions, and a number of references are given. The following references may also be useful: Woolmer, *Progrès méd.*, 1945, **73**, 407; Gordon, R. A., *Canad. med. Ass. J.*, 1943, **49**, 478; Dirceu, H., Clerq, F., and Duprez, A., *Acta clin. belg.*, 1946, **1**, 150. Although its effect in status asthmaticus is sometimes dramatic, like that of other drugs which are useful in this condition, intravenous procaine is, however, no panacea. It has been suggested that its effect in allergic conditions is due to its antihistamine-like action, but there is no proof that this is the correct explanation.

The usual dosage in asthma is 4 ml. of 1% procaine given slowly intravenously, or 0.1% procaine in saline given as a drip up to a maximum of 500 ml. in 30 minutes.

Primary Carcinoma of the Other Breast

Q.—*Is there a higher incidence of primary carcinoma in the remaining breast in those women who have already undergone one successful operation for cancer of the breast, as compared with a control group? If the incidence is approximately equal in both groups, can this be taken as evidence in favour of an intracellular (genetic) origin for breast cancer, as opposed to any extracellular carcinogenetic influence? If the second carcinoma arises purely fortuitously, would not the incidence of cancer in those with only one breast be approximately half that of those who still possess two?*

A.—There does not seem to be on record any specific statistical study of the incidence of primary carcinoma in the remaining breast after successful radical mastectomy for carcinoma of the opposite breast. Clinical experience does not lead to the assumption that this is likely. If there is no greater incidence than in a control group it would be difficult to say what this means; it is generally considered that some ovarian hormonal influence is at work in the genesis of breast cancer. The disease starts in the ducts of the breast, but some extra-mammary influence is believed to be at work. There must also be borne in mind the question of "immunity" and resistance developing in a patient who has been treated successfully for cancer; if this happens it would presumably affect the possibility of malignancy supervening in the remaining breast.

Homologous Serum Jaundice

Q.—*Were cases of serum jaundice reported as a result of inoculating many recruits with the same syringe? At a training centre I used to inoculate several hundred recruits in an hour or two. A fresh needle was employed for each injection, but the same syringe was used for dozens of cases.*

A.—Homologous serum jaundice was reported in British and American troops after inoculation with a yellow-fever vaccine which contained small amounts of human serum. An outbreak occurred among troops after the injection of convalescent mumps serum, and several groups of workers reported a high incidence of jaundice in the Service V.D. clinics; this was controlled when care was taken to sterilize syringes and needles between injections (Salaman *et al.*, *Lancet*, 1944, **2**, 7). The transfer of the causative agent of serum jaundice has not apparently been reported after injections of T.A.B. vaccine and the like, but an unduly high incidence has been noted in a diabetic clinic. Usually it has been presumed that only the needle is contaminated after subcutaneous or intramuscular injections, but the recent report by Evans and Spooner (*Journal*, July 22, 1950, p. 185) indicates that the syringe itself may be contaminated by back suction when the needle is being removed. The risk of transferring infection by the "separate needle, common syringe" technique is obviously small in this country except possibly for the risk of conveying homologous serum jaundice. Until other means of overcoming this are devised, it may be advisable to sterilize both syringe and needle before each injection. For a fuller discussion of this point an annotation in the same issue of the *Journal* should be consulted (p. 204) and a letter from Sir Alexander Fleming, F.R.S., in the *Journal* of August 5 (p. 365).

Intravenous Iron

Q.—*Please outline the latest information on therapeutic intravenous iron with reference to the indications, contraindications, dosage, and the technique of administration.*

A.—A number of satisfactory proprietary preparations of saccharated iron oxide suitable for intravenous injection are now available in this country. Provided that excessive doses are avoided, there are no contraindications to this form of treatment, which is as well tolerated by children as by adults. Intravenous iron is indicated for those cases of hypochromic anaemia which do not respond to adequate doses of iron by mouth, either through failure of absorption, as in coeliac disease and idiopathic steatorrhoea, or because orally administered iron provokes severe gastro-intestinal symptoms. It has also been shown that the anaemia accompanying certain chronic toxic or infective states, such as rheumatoid arthritis, which is usually refractory to iron given by mouth, may be corrected by parenteral therapy. The dose for an adult is 200 mg. daily or every other day. However, it is advisable to start with a dose of 50 mg.; 100 mg. is given on the second day, and the full dose thereafter. The technique of administration is simple, the aim being to avoid any deposition of iron outside the wall of the vein, where it produces intense irritation. As the solution is very dark in colour it is difficult to detect a small quantity of blood in the barrel of the syringe on withdrawing the plunger; 3–5 ml. of blood should therefore be withdrawn before the injection is made. The subject was discussed fully in an annotation in the *Journal* of May 13 (p. 1127).

Inhibition of Micturition

Q.—*Some male patients complain that they are unable to begin the act of micturition unless they are in more or less complete privacy. They are incommoded when the only opportunity for emptying the bladder is in a crowded lavatory. There is no organic lesion to account for this difficulty. It is a psychological trouble, not uncommon among shy, sensitive males, micturition presenting no difficulty to them at home or in relative privacy. Has modern psychotherapy any assistance to offer?*

A.—Such a condition must be regarded in the nature of a conditioned reflex, and is found to be due to some experience of shame or threats connected with the genital organs in childhood, usually concerning micturition, masturbation, or exhibitionism. The forms of treatment are: (*a*) Reconditioning by gradually and stage and by stage getting accustomed to the presence of other people. The effectiveness of this is doubtful. Some men got over it spontaneously under Army conditions, others did not. (*b*) Suggestion, under hypnosis or otherwise, in an attempt to break the vicious circle, is often more effective. (*c*) Discovery of the "traumatic" cause and release of the pent-up emotion by analysis is certainly the most effective and

permanent method, but it takes more time. It is, however, well worth while if such treatment can be obtained in view of the distress suffered by many of these patients—distress far beyond the mere inconvenience, for the situation arouses to some extent the original feeling of shame.

Domiciliary Treatment of Tuberculosis

Q.—*Is there any antibiotic treatment which is worth trying in general practice for a case of chronic fibrocaseous pulmonary tuberculosis? The patient I have in mind is a man of 55 with chronic cavities and a positive sputum; he has been treated with P.A.S. for a long time. Could streptomycin be given while he is at home, or would "aureomycin" or "chloromycetin" or any other antibiotic be worth a trial?*

A.—Streptomycin is the only antibiotic that might benefit the patient, but this should not be given at home unless there are facilities for determining the streptomycin sensitivity of the tubercle bacilli in the patient's sputum. An exception to this general rule is the use of the drug as a palliative measure in cases of painful tuberculous laryngitis. From the description of the case it is unlikely that any permanent benefit will result from the use of streptomycin.

Treatment of Defective Fat Absorption

Q.—*Is "sorethitan mono-oleate" of proved value in the treatment of deficient fat absorption? Is it safe to take over long periods at the dose recommended—6 g. daily? My particular interest is in cases of subtotal gastrectomy with failure to gain weight.*

A.—Sorbitan polyoxyethylene mono-oleate (Tween 80) appears to be effective in improving fat absorption in certain cases, including the post-gastrectomy syndrome (C. M. Jones, P. J. Culver, G. D. Drummey, and A. E. Ryan (1948), *Ann. int. Med.*, **29**, 1), although it seems unlikely that the effect is due to any change in emulsification, since this is commonly normal in such cases. Extensive studies on the toxicity of this substance have also been carried out by P. J. Culver in Boston and by L. Emmett Holt, jun., in New York. In human subjects 4.5–6.0 g. per person per day have been administered for periods of up to two years and no ill effects could be demonstrated. Similar investigations were carried out in children; 50 mg. of "Tween 80" per gramme of fat ingested caused no demonstrable ill effects in premature infants. Care should be taken to see that unspecified impurities are not present with the sorbitan polyoxyethylene mono-oleate, since these may be toxic.

Artificial Parthenogenesis

Q.—*I should be interested to know whether any experiments on artificial parthenogenesis have been, or are being, carried out in this country.*

A.—It is not clear whether the questioner is referring to experiments on artificial parthenogenesis in mammals or in invertebrates. Very little work has been done anywhere on artificial parthenogenesis in mammals, but a great deal has been done on artificial parthenogenesis in invertebrates such as the sea-urchin. A useful and comprehensive review of this work was published in the British journal, *Biological Reviews* (1941, **16**, 291), by Dr. Albert Tyler.

Dioxyamidopyrine in Asthma

Q.—*A new proprietary for the relief of asthma is said to contain dioxyamidopyrine. Is this drug likely to lead in some cases to agranulocytosis? What is the action of the drug, and have any clinical trials been reported?*

A.—The proprietary preparation which this correspondent probably has in mind is made up of a large number of ingredients, and no clinical trials with it have been reported in the literature. Some of these ingredients are of known value in relaxing bronchial spasm, while others are valueless in this respect. This type of polypharmacy is to be deprecated. Reliance should be placed on official preparations of adrenaline, ephedrine, isoprenaline, or theophylline and ethylenediamine, each of which will be found to be just as effective as—and usually cheaper than—proprietary preparations containing many ingredients. One of the constituents of this particular preparation is a small dose of dioxyamidopyrine. It is true that amidopyrine has been found on occasion to produce agranulocytosis, and has in consequence acquired an unenviable reputation. However, the danger of using amidopyrine is probably considerably exaggerated. At one time almost all patent headache powders, which were consumed by thousands of people daily, contained a little amidopyrine, and yet agranulocytosis remained uncommon. Still, there is no point in including amidopyrine in prescriptions when other analgesics will do equally well without incurring this objection.

Thrush and Myasthenia Gravis

Q.—*Can you suggest any treatment for a thick white deposit on the hard palate and tongue of a woman aged 60 suffering from myasthenia gravis? Her symptoms are well controlled by prostigmin, but the condition of the oral mucous membrane has been present for about four years, and does not react to any ordinary local treatment.*

A.—It is difficult to recommend treatment for this condition in the absence of a precise diagnosis. The description suggests extensive thrush, which occurs in debilitated states, and which may here be related to the dysphagia. In some elderly patients this infection may clothe the entire buccal mucosa with a thick white deposit which is most resistant to treatment. Swabbing the mouth gently but thoroughly with a 5% solution of sodium metabisulphite and afterwards with borax, soda, and glycerol is usually effective. The possibility of leukoplakia must be considered; and, if lichen planus seems likely, a trial of arsenic is worth while.

NOTES AND COMMENTS

Prophylaxis Against Syphilis.—Dr. Arthur S. Wigfield (Worcester) writes: In your answer under this heading ("Any Questions?" July 22, p. 231) it is stated that "even 200,000 units to 300,000 units (of penicillin) taken by mouth within a few hours has been reported as preventing infection." If this report relates to clinical experiment it seems pertinent to ask by what method these "protected" patients were shown to be incubating syphilis. While not wishing to dispute the veracity of such an assertion, I would nevertheless like to express my doubts of the wisdom of making it under the heading of "Any Questions?" The answers to "Any Questions?" are primarily of general interest. Your brief dissertation on the prophylaxis against syphilis is presumably designed not for competent venereologists but for general practitioners. How many general practitioners will now administer 300,000 units of penicillin by mouth in order to allay the fears of apprehensive patients? If none, why mention this dangerous practice without due warning? The danger of such a procedure would seem to be not so much the possibility of masking syphilis as the creation of a fool's paradise in which further transmission of the disease might occur. In mentioning the "best" prophylaxis against syphilis the total dose of four million units of penicillin should be coupled with a reasonable duration of its administration—i.e., seven to fourteen days. It is difficult to escape the conviction that such "protected" patients should be regarded as sero-negative primary cases and followed up for two years. Is it not wiser to persuade these patients to refrain from coitus for three months and ask them to report for examination then?

Corrections

Dr. J. W. Dundee (Walton, Liverpool) has written to point out that in the Medical Memorandum "Acquired Sensitivity to Thiopentone" (August 5, p. 332) the dose of thiopentone given at the first operation was 0.3 g., not 0.3 mg.

In the report (August 5, p. 358) of a discussion at the Section of Tropical Medicine during the Annual Meeting of the B.M.A. in Liverpool we wrongly attributed Colonel E. H. Vere-Hodge's remarks to Dr. R. F. Vere-Hodge. Colonel Vere-Hodge has written to point out that his statement that santonin was non-toxic was qualified by the words "in therapeutic doses."

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